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Social and Emotional Processing in Borderline Personality Disorder

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Declaration of authorship

I confirm that:

1. This thesis has been wholly composed by myself

2. The work presented here is my own

3. The work presented here has not been previously submitted for any other degree or qualification

Signed: Katri Niiol

Date: 19/10/2015

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Glossary of abbreviations

ANOVA – analysis of variance

BET – brain extraction tool

BOLD – blood oxygen level dependent

BPD – borderline personality disorder

CBT – cognitive behavioural therapy

CEN – central executive network

CTQ – Childhood Trauma Questionnaire

DARTEL – diffeomorphic anatomical registration using exponentiated lie algebra

DBT – dialectical behavioural therapy

DCM – dynamic causal modelling

DMN – default mode network

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, 4th edition

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, 5th edition

ER – Emotion Recognition test

FAN – Fear Anger Neutral test

FDR – false discovery rate

fMRI – functional magnetic resonance imaging

FOV – field of view

FPT – Faux Pas test

FWE – family wise error

HAM-D – the Hamilton Rating Scale for Depression

ICA – independent component analysis

MASC – Movie for the Assessment of Social Cognition

MBT – mentalisation-based treatment

MCFLIRT – motion corrected FMRIB's linear image registration tool

MELODIC – multivariate exploratory linear decomposition into independent components

MNI – Montreal Neurological Institute

MPFC – medial prefrontal cortex

MP-RAGE – magnetisation-prepared rapid gradient-echo sequence

MRI – magnetic resonance imaging

MTL – medial temporal lobe

NART – National Adult Reading Test

NNL – NordicNeuroLabs

OFC – orbitofrontal cortex

PANSS – the Positive and Negative Syndrome Scale

PFA – Pictures of Facial Affect

PET – positron emission tomography

PPI – psychophysiological interactions

RAPFA – Revised Adult Personality Functioning Assessment

RME – Reading the Mind in the Eyes Task

SCID-I – the Structured Clinical Interview for DSM-IV Axis I Disorders

SCID-II – the Structured Clinical Interview for DSM-IV Axis II Personality Disorders

SFT – schema focused therapy

sMRI – structural magnetic resonance imaging

SN – salience network

SPM – statistical parametric mapping software

TE – echo time

ToM – theory of mind

TR – repetition time

VBM – voxel based morphometry

YMRS – the Young Mania Rating Scale

ZAN-BPD – the Zanarini Rating Scale for Borderline Personality Disorder

Abstract

Objective

Borderline Personality Disorder (BPD) is a common and serious mental illness, associated with severe emotional dysregulation, a high risk of suicide and self-harm. Those with a diagnosis of BPD often display difficulties with social interaction, making daily life problematic, and sufferers can struggle to form and maintain interpersonal relationships. Childhood trauma is believed to contribute to the development of BPD, however the mechanism by which childhood trauma increases risk for specific symptoms of the disorder is not well understood. Here, we investigate the ability of participants with a diagnosis of BPD to make social judgements and recognise emotions from facial stimuli. We also explore the relationship between childhood trauma, brain structure, and brain activation in response to emotional stimuli.

Methods

Individuals with a diagnosis of borderline personality disorder, as well as matched healthy controls, were recruited to take part in a neuropsychology study of emotion recognition and social judgement from faces. Participants also underwent a magnetic resonance imaging (MRI) scan, during which data was collected for analysis of brain structure, and brain function in response to

emotional faces. In addition, all participants completed a structured clinical interview and the Childhood Trauma Questionnaire (CTQ).

Results

Individuals with a diagnosis of BPD were less well able to correctly identify facial emotions than healthy control participants ($p < 0.001$), with a particular deficit in the recognition of disgust ($p = 0.001$). Those with BPD also had difficulty making appropriate social judgements about others from their faces, and between group differences were greatest for judgements of approachability ($p = 0.004$) and trustworthiness ($p = 0.014$). Significant correlations were identified between CTQ scores and performance on both tasks in the BPD group.

Although no structural brain differences were noted between the BPD group and healthy controls, we found that brain activation correlated to childhood trauma in midbrain, pulvinar and medial frontal gyrus to fearful (versus neutral) faces. There was a significant association between incidence of abuse in childhood and psychotic symptoms in adulthood. In addition, there was a significant correlation between midbrain activation and reported psychotic symptoms in the BPD group, suggesting a potential relationship between childhood trauma, midbrain activity and the development of psychotic symptoms in those with a diagnosis of BPD.

Conclusion

Abuse in childhood is associated with impaired social and emotional function, as well as increased activation of a network of brain regions in response to emotional stimuli in BPD. Brain abnormalities in BPD appear to be confined to functional activation changes, rather than structural changes, in regions associated with emotional and social information processing. In addition, childhood trauma is correlated with increased psychotic symptoms in adulthood. These results provide striking evidence for the involvement of childhood adversity in the development of symptoms of BPD, and suggest a possible mechanism by which psychotic symptoms may occur.

Summary

Borderline Personality Disorder (BPD) is a common and serious mental illness, associated with severe emotional dysregulation, a high risk of suicide and self-harm. Childhood trauma is believed to contribute to the development of BPD, however this is not well understood. Here, we investigate the ability of participants with a diagnosis of BPD to make social judgements and recognise emotions from faces. We also explore the relationship between childhood trauma, brain structure, and brain function.

Individuals with a diagnosis of BPD, as well as matched healthy controls, were asked to identify emotions and make judgements about people from pictures of faces on a computer screen. Participants also underwent a magnetic resonance imaging (MRI) scan, during which data was collected for analysis of brain structure, and brain function in response to emotional faces. In addition, all participants completed a structured clinical interview and the Childhood Trauma Questionnaire (CTQ), which is a self-report measure of adverse events in childhood.

Those with a diagnosis of BPD were less well able to correctly identify facial emotions than healthy control participants, with a particular deficit in the recognition of disgust. Those with BPD also had difficulty making appropriate social judgements about others from their faces, especially for judgements of approachability and trustworthiness. We found that greater childhood adversity

corresponded to poorer performance in both of the tasks. We also found that brain activation correlated to childhood trauma in several brain areas involved in social and emotional processing, and there was a significant association between incidence of abuse in childhood and symptoms of the disorder in adulthood.

These results provide striking evidence for the involvement of childhood adversity in the development of symptoms of BPD, and provide evidence for the development and use of early intervention strategies in young people at high risk for the development of the disorder.

1. Introduction

1.1. Introduction to Borderline Personality Disorder

1.1.1. What is Borderline Personality Disorder?

Borderline Personality Disorder (BPD) is a common, serious and complex psychiatric illness. The DSM-5 states that the main features of BPD are a pervasive pattern of instability in interpersonal relationships, self image and affects, as well as impulsive behaviour (American Psychiatric Association 2013). Clinical symptoms of the disorder include emotional dysregulation, self-injury and suicidal tendencies, with 60%-70% of those with BPD attempting suicide (Oldham 2006), and the rate of successful suicide 50 times greater in this group than that of the general population (Lieb 2004).

Individuals with a BPD diagnosis find establishing and maintaining interpersonal relationships, as well every-day social interaction extremely difficult (Lis and Bohus 2013). Those with a diagnosis of BPD often report that their personal relationships are intense, chaotic and conflicted (Linehan 2003), and people suffering from the disorder have been described as having difficulty being alone and seeking out intense contact with others (Gunderson and Ridolfi 2001). Studies have shown that individuals with a BPD diagnosis have fewer

social interactions than do healthy controls, and that these interactions are more likely to be experienced as negative, for example ambivalent, sad, by sufferers (Stepp et al 2009, Russell et al 2007). As a result, sufferers often find daily functioning extremely challenging and BPD is recognised as being a highly disabling disorder (Grant et al 2008).

1.1.2. Epidemiology of BPD

BPD is thought to affect in the region of 1-3% of the general population, and is the most frequently diagnosed personality disorder (Carpenter and Trull 2013), contributing to up to 25% of all psychiatric inpatient contacts and 10% of outpatient appointments (Leichsenring et al 2011). It is believed that the incidence of BPD symptoms within the general population could be even greater than that commonly reported, with a large population study in the United States reporting the presence of BPD in 5.6% of the representative adult population sample interviewed (Grant et al 2008). Underestimation of the condition may be due to several factors, including reluctance of sufferers to seek medical assistance, or misdiagnosis.

The age of onset of BPD is typically between ages 18-25, consistent with the general characteristics of personality disorders, and in three quarters of cases BPD will be diagnosed by age 30 (Gunderson 2009). Although diagnosis of BPD in adolescents has been allowed since the release of the Diagnostic and

Statistical Manual of Mental Disorders IV (DSM-IV) in 2000, diagnosis before the age of 18 is still uncommon. However studies have shown that the prevalence, reliability and validity of the disorder in adolescents is comparable with that of adult populations (Miller et al 2008, Becker et al 2002). The vast majority of clinical studies report that BPD is far more common in females than in males, normally being reported at between 70%-80% female (Gunderson 2009, Paris 2005, Lieb et al 2004). However this trend does not appear to be present in community samples, which report that there is no difference in the prevalence of BPD between men and women (Grant et al 2008, Lenzenweger et al 2007, Torgersen et al 2001). This discrepancy between clinical and community samples is considered to be due to fewer men seeking medical assistance for their symptoms.

1.1.3. Diagnosis and comorbidity of BPD

Personality disorders are described by the DSM-IV as enduring patterns of inner experience and behaviour that deviate markedly from what is expected. Personality disorders are pervasive, inflexible, and stable over time, and usually have their onset in adolescence or early adulthood.

The DSM-IV states that to receive a diagnosis of BPD, an individual must meet five of nine criteria (American Psychiatric Association 2000), as follows:

1. Frantic efforts to avoid real or imagined abandonment.

2. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation

3. Identity disturbance: markedly and persistently unstable self-image or sense of self

4. Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating).

5. Recurrent suicidal behaviour, gestures, or threats, or self-mutilating behaviour

6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)

7. Chronic feelings of emptiness

8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights)

9. Transient, stress-related paranoid ideation or severe dissociative symptoms

Although in the current work the DSM-IV was used for diagnosis, a newer edition of the manual, the DSM-5, was published in 2013. In the newer version

of the DSM, the criteria for BPD, and the way in which it is diagnosed, have changed. Now, in order to diagnose BPD, the following criteria must be met:

A. Significant impairments in personality functioning manifest by:

1. Impairments in self functioning (a or b):

a. Identity: Markedly impoverished, poorly developed, or unstable self-image, often associated with excessive self-criticism; chronic feelings of emptiness; dissociative states under stress.

b. Self-direction: Instability in goals, aspirations, values, or career plans.

AND

2. Impairments in interpersonal functioning (a or b):

a. Empathy: Compromised ability to recognise the feelings and needs of others associated with interpersonal hypersensitivity (i.e., prone to feeling slighted or insulted); perceptions of others selectively biased towards negative attributes or vulnerabilities.

b. Intimacy: Intense, unstable, and conflicted close relationships, marked by mistrust, neediness, and anxious preoccupation with real or imagined abandonment; close relationships often viewed in extremes of idealization and devaluation and alternating between over involvement and withdrawal.

B. Pathological personality traits in the following domains:

1. Negative Affectivity, characterized by:

a. Emotional liability: Unstable emotional experiences and frequent mood changes; emotions that are easily aroused, intense, and/or out of proportion to events and circumstances.

b. Anxiousness: Intense feelings of nervousness, tenseness, or panic, often in reaction to interpersonal stresses; worry about the negative effects of past unpleasant experiences and future negative possibilities; feeling fearful, apprehensive, or threatened by uncertainty; fears of falling apart or losing control.

c. Separation insecurity: Fears of rejection by – and/or separation from – significant others, associated with fears of excessive dependency and complete loss of autonomy.

d. Depressivity: Frequent feelings of being down, miserable, and/or hopeless; difficulty recovering from such moods; pessimism about the future; pervasive shame; feeling of inferior self-worth; thoughts of suicide and suicidal behaviour.

2. Disinhibition, characterized by:

a. Impulsivity: Acting on the spur of the moment in response to immediate stimuli; acting on a momentary basis without a plan or

consideration of outcomes; difficulty establishing or following plans; a sense of urgency and self-harming behaviour under emotional distress.

b. Risk taking: Engagement in dangerous, risky, and potentially self-damaging activities, unnecessarily and without regard to consequences; lack of concern for one's limitations and denial of the reality of personal danger.

3. Antagonism, characterized by:

a. Hostility: Persistent or frequent angry feelings; anger or irritability in response to minor slights and insults.

C. The impairments in personality functioning and the individual's personality trait expression are relatively stable across time and consistent across situations.

D. The impairments in personality functioning and the individual's personality trait expression are not better understood as normative for the individual's developmental stage or socio-cultural environment.

E. The impairments in personality functioning and the individual's personality trait expression are not solely due to the direct physiological effects of a substance (e.g., a drug of abuse, medication) or a general medical condition (e.g., severe head trauma).

These criteria cover a large number and wide range of behaviours and symptoms and, as a result, it is possible that two individuals, each with a BPD diagnosis, may have only one of these behaviours in common. Many of the symptoms described also overlap with several Axis I conditions (Paris 2007). This, along with the complex nature of the disorder and varying severity of symptoms, can make diagnosing BPD difficult.

The name borderline personality disorder is derived from the original conceptualisation of the condition, specifically that sufferers lay on the borderline between psychosis and neurosis (Paris 2007), again illustrating the variety of symptoms experienced by those with a BPD diagnosis. Such complexity may also contribute to the high number of sufferers with one or more comorbid diagnoses. One US population study found that 84.5% of respondents with a diagnosis of BPD also met criteria for one or more 12 month Axis I diagnosis (Lenzenweger et al 2007), and other studies have reported even higher incidences of comorbidity, with Zanarini et al (1998) reporting a comorbid mood disorder diagnosis in over 95% in an inpatient sample of people with a BPD diagnosis, the most common being major depression (83%). High rates of comorbidity were also noted for substance use disorders (64%), anxiety disorders (88%, including PTSD at 56%) and eating disorders (53%) in those with a diagnosis of BPD. Grant et al (2008) also reported significant lifetime associations between BPD and bipolar I and II disorders, as well as narcissistic personality disorder and schizotypal personality disorder in a population study of over 34000 people.

1.1.4. Aetiology of BPD

The exact causes of BPD are not known, but both genetic and environmental risk factors are believed to contribute to its aetiology (Riechborn-Kjennerud et al 2013, Distel et al 2009, Distel et al 2008). Genetic concordance rates for BPD in twins has been reported as 38% in monozygotic twins and 11% in dizygotic twins (Crowell et al 2009), and 42%-68% of variance in the disorder has been attributed to genetic factors (Gunderson 2011). Although specific genetic risk factors for BPD have not been identified, genes linked to the serotonergic and dopaminergic systems have been implicated as potentially contributing to the disorder (Riechborn-Kjennerud 2010, Crowell et al 2009). A recent review focussing on gene-environment studies in BPD found that there was greatest evidence to support a gene-environment (rGE) correlation model for BPD and adverse events including sexual assault, violent assault and divorce/break up (Carpenter et al 2013). Genes influencing BPD features appear to increase the likelihood of exposure to such events, however it is not yet possible to determine the direction of this association. Carpenter et al (2013) also point out that the majority of gene-environment studies in BPD suffer from methodological shortfalls, which cannot be ignored, such as small sample sizes and imprecise measurements. Therefore, while it appears to be the consensus that both genetic and environmental factors contribute to the development of BPD, there is no clear picture of how these interact.

It has been suggested that environmental features during development can lead to some of the difficulties and behaviours elicited by those with a diagnosis of BPD. For example, the extreme emotional lability that is characteristic of BPD may be established and maintained by the caregiving environment during development (Crowell et al 2009). Additionally, a large proportion of BPD sufferers report adverse childhood events, and is it widely regarded that trauma in childhood is associated with later development of BPD (Ball and Links 2009, Zanarini 1997, Herman 1989). Ball and Links (2009) investigated childhood trauma may as a causative factor in the development of BPD by examining previous literature according to Hill's (1984) criteria for a causal relationship. They found that overall, the evidence points to a causal relationship between childhood trauma and BPD, and that it is likely that adverse events in childhood do contribute to the development of BPD (table 1.1).

Criterion	Definition	Identified in BPD?
Strength of association	Is there is a strong association between the two variables in question?	Yes
Temporality	Does the proposed causal variable occur at an earlier time than the outcome variable (in this case, does trauma occur before the onset of BPD)?	Not clear
Dose-response	Does the outcome variable increase in severity as the independent variable (trauma) increases in severity?	Yes
Specificity	Are the proposed causal variable and outcome measure specific to one another (in this case is childhood trauma specific to BPD)?	Not clear
Consistency	Is the relationship between variables consistent across studies?	Yes
Epidemiologic and biologic plausibility	Does the proposed relationship make epidemiologic and biologic sense?	Not studied due to insufficient literature
Analogy	Is the proposed relationship comparable to any other causal relationships?	Yes

Table 1.1. Summary of Ball and Links (2009) investigation into a causal relationship between childhood trauma and BPD.

Brain development and vulnerability to environmental adversity

Normal brain development occurs over a number of stages, during which differing brain regions have different courses of development. This complex and extended period of brain development, which continues to the end of the second decade of life in humans, allows for several distinct periods of vulnerability. Brain development can be broadly split into two categories – prenatal and postnatal. Prenatal brain development takes place before birth, and includes the production, migration and branching of neurons to establish suitable connections, a process heavily influenced by numerous growth factors (Stiles and Jernigan 2010). These events provide the basic structure of the brain and nervous system, and initial patterning of neurons; however the mature structure and organisation of the brain emerges gradually, over a protracted period of time during postnatal development. The process of refining brain structure and function is dependent on interactions between genetic programming and the environment. External factors can differentially affect brain topography, categorising development as either experience-expectant or experience-dependent (Greenough et al 1987).

Experience-expectant development incorporates normal, ubiquitous environmental stimuli into development, and such experiences are often essential to facilitate proper brain development. The process of experience-

expectant development involves critical periods, during which appropriate stimuli must be experienced for normal development (Stiles and Jernigan 2010, Andersen 2003). For example visual, auditory and sensory stimuli are required for the development of the senses. During critical periods an excess of neuronal connections – synapses - is produced, followed by elimination of unnecessary connections. Important connections are strengthened while those that do not contribute to the critical process are weakened.

Experience-dependent development involves the incorporation of more unique, person specific stimuli into brain development. This process involves sensitive periods, during which stimuli, such as stress, infection, drug use, may have characteristic effects on, for example, behaviour or physiology, dependent on the time of exposure (Andersen 2003).

Certain adverse events in early life, such as parental separation or maltreatment can therefore have an effect on brain development, and may contribute to the development of psychiatric disorders and their symptoms.

These effects have been investigated using animal models of early life stress. Several different models exist, but all focus on maternal care, and the relationship between mother and offspring, with common models involving maternal separation or deprivation (McEwen 2009). Strong maternal behaviour produces “confident” young, likely to readily explore new environments. Such offspring also appear less emotionally reactive than those who have been

subject to periods of maternal separation. Rough maternal handling of pups is associated with increased attachment to, rather than avoidance of the mother, and may represent a model of childhood abuse (McEwen 2009). Several factors can influence the effects of early life stress in animals, including length and type of stress, and period of development during which stress is experienced (Harrison and Baune 2014). Just as critical stages of development occur in humans, the same appears to be true of the animal models studied, and stressors that are present during such times have a far greater effect on behaviour than the same stressor experienced during a non-critical development stage (Harrison and Baune 2014). As well as behavioural changes, early life stress in animal models has been shown to have an effect on metabolism, nociception, immune response and neurotransmitter systems, as well as on physical brain structure and plasticity (Marco et al 2015).

Many similar deficits and abnormalities are described in BPD pathology, and it is likely that exposure to adverse events in childhood impacts upon the way in which the brain develops in BPD (Fonagy 2009), although specific periods of vulnerability have not yet been identified for the development of the disorder. Interestingly, pharmacological interventions and environmental enrichment can modulate the effects of early life stress in animals (Harrison and Baune 2014, McEwen et al 2009), suggesting that the same may be possible in humans.

1.1.5. Treatment of BPD

Until relatively recently (the past 15 years or so) a diagnosis of BPD was predominantly viewed as a "wastebasket" diagnosis, with no effective treatment. It was widely the belief that there was little or no hope of recovery for those suffering from the disorder (Sanislow et al 2012).

Although this opinion has largely changed for the better, the effectiveness of drug therapy in BPD is still disputed. Individuals with a diagnosis of BPD are often treated with a combination of drugs to alleviate the various symptoms of the disorder. Antidepressants, mood-stabilisers, antipsychotics and neuroleptics are commonly prescribed to those with BPD (Olabi and Hall 2010), dependent on the specific symptoms experienced. Antidepressants help to alleviate the depressive symptoms often experienced by those with a diagnosis of BPD and, as previously mentioned, major depression is co-occurring in the vast majority of people with the disorder. Mood-stabilisers may help with affect regulation in BPD. This type of medication is used in the treatment of bipolar disorder, which has many clinical similarities to BPD (Bayes et al 2014, Zimmerman and Morgan 2013). Antipsychotics are commonly prescribed to those with a diagnosis of BPD to treat symptoms pertaining to psychosis, such as delusions and hallucinations, as well as impulsive behaviour. However, it is commonly reported that, in the effective treatment of BPD, it is psychotherapy and not pharmacotherapy that proves most beneficial, and psychological

therapies are regarded as the first-line treatment for BPD by the American Psychiatric Association (2001) and experts in the field (Biskin and Paris 2012, Stoffers et al 2012, Paris 2010, Zanarini 2009).

Psychotherapies commonly employed in the treatment of BPD include mentalisation based treatment (MBT) and cognitive behavioural therapies, specifically dialectical behaviour therapy (DBT) and schema focused therapy (SFT). While DBT is currently the most widely utilised therapy, all of these psychotherapies have been shown to be effective in the treatment of BPD in terms of psychopathology and hospital utilisation compared to treatment as usual (Biskin and Paris 2012, Kahl et al 2012, Paris 2010, Zanarini 2009). A brief summary of each is given below:

Dialectical behaviour therapy (DBT): DBT was originally developed from standard cognitive behavioural therapy (CBT) for the treatment of suicidal and self-injurious behaviours, and later developed to become a treatment for BPD (Rafaeli 2009, Linehan 1993, Linehan et al 1991). DBT is based on the theory that emotion dysregulation, caused by an interaction between biological traits and adverse childhood environment is at the core of the common behaviours associated with BPD (Zanarini 2009), and the therapy has a focus both on acceptance (of one's emotional pain) and change (altering the dysfunctional behaviours as well as the stressors which may trigger them) (Lynch et al 2007). DBT is an intensive therapy that includes both individual and group therapy

sessions, as well as telephone support as required from a therapist (Bloom et al 2012).

Schema focused therapy (SFT): A schema is a cognitive network of thought and ideas, and a maladaptive schemas can lead to a negative sense of self, others and the environment (Sempertegui et al 2013). SFT teaches recipients a range of techniques to address dysfunctional or undesirable behaviours, emotions and cognition (Kahl et al 2012). SFT aims to facilitate change by validating and encouraging the understanding of events that may have led to a particular schema view (Rafaeli 2009). The techniques learned can be applied to everyday life in order to challenge and change the maladaptive schema.

Mentalisation based treatment (MBT): Mentalising is the ability to make sense of ourselves and others, by way of understanding our own feelings and thoughts, as well as those of the people around us (Bateman and Fonagy 2010). This process is essential for effective social interaction, and MBT focuses on encouraging awareness of behaviour, and recognising how emotional state can drive a response in a given situation (Eizirick and Fonagy 2009). Those undertaking MBT are encouraged to understand their own and others' behaviour in terms of their thoughts, feelings, wishes and desires (Fonagy and Luyten 2009), allowing them to stabilise their own emotional responses.

1.1.6. Prognosis of BPD

In contrast to the often pessimistic view of personality disorders, there is good evidence that the symptoms of BPD lessen with time, and research suggests that individuals with a diagnosis of BPD tend to achieve remission by late middle age. Two longitudinal studies noted that the number of individuals in which BPD had remitted increased with each time point (Zanarini et al 2003, Paris and Zweig-Frank 2001). Both studies reported similar over-all remission rates of approximately 75%.

1.2. The social brain – relevance to BPD

1.2.1. Face processing

Faces are the source of a wealth of social information. By viewing only a person's face, we can infer information about the mood, level of interest and intentions of that person; and the majority of us will spend more time looking at faces than at any other type of object in our lifetime (Haxby et al 2000).

Bruce and Young (1986) first introduced a model of face processing, and proposed that there are at least seven types of information, or codes, that can be gleaned from faces. The proposed codes are as follows:

1. Pictoral – information derived from viewing a static picture of a face

2. Structural – arrangement of facial features which enables distinction of one face from another

3. Visually derived semantic – information about the person, for example age, sex, and even attributes such as intelligence

4. Identity specific semantic – for familiar faces, specific information regarding recognition, such as where the person is usually encountered

5. Name – for familiar faces, associating a name with a face

6. Expression – information about the mood or emotion of a person

7. Facial speech - information derived from movements of the lips and tongue

Bruce and Young (1986) proposed a branching, hierarchal system for face processing, beginning with structural encoding. This structural perception is then further processed for person identity, and this is processed further to

retrieve person information, such as name. In this model, a separate system is proposed for the processing of facial expression, speech analysis and eye gaze following structural encoding, so that each aspect of face processing is managed by a distinct neural system (figure).

This model of face processing was updated by Haxby et al (2000), who proposed that changeable (expression, eye gaze) and invariant (structure, identity) aspects of faces have distinct core neural processing systems, but that these interact with other systems to achieve complete face perception (figure).

These codes allow for face and/or person recognition, and demonstrate the volume of information that is evoked from each face we encounter. It is evident, then, that efficient face processing is key in effective social interaction of all kinds.

The development of neuroimaging techniques has allowed for investigation of the neural mechanisms involved in processing such a myriad of information, with a region of the lateral fusiform gyrus found to be so specialised for face perception that it has been dubbed the fusiform face area (Kanwisher and Yovel 2006, Kanwisher et al 1997). This area of the brain consistently shows greater activation in response to viewing faces than in response to viewing other non-face objects (Haxby et al 2000), as well as faces of animals, and other human body parts (Kanwisher et al 1997). However, face perception involves a range of

brain areas, recruited to process specialised information relevant to social cognition.

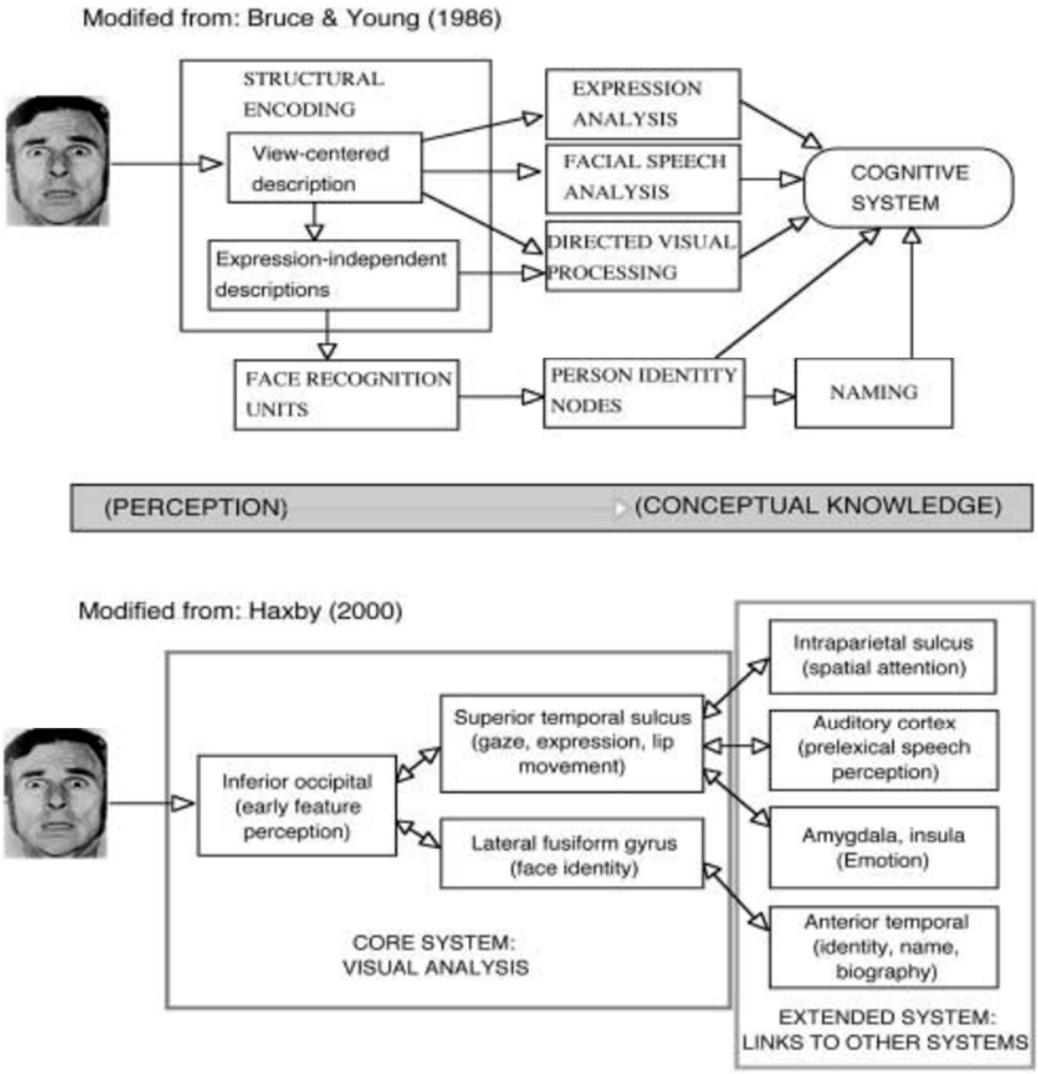


Figure 1.1. The top of the figure represents the model of face perception proposed by Bruce and Young (1986), depicting separate neural systems for each process involved in identity and emotion recognition. The bottom of the figure represents the model proposed by Haxby et al (2000), in which two core neural systems interact with others reciprocally to achieve identity and emotion perception. Figure taken from Adolphs 2002.

Facial expressions are extremely important in social cognition, as they allow us to interpret the emotions of another person. There are six basic facial emotions – anger, fear, happiness, sadness, surprise, disgust – which are universally recognisable, regardless of culture (Ekman and Friesen 1971). Ekman and Friesen (1978) were the first to develop a system for measuring these expressions, known as the Facial Action Coding System, in which they documented all of the muscle movements associated with particular emotions. This approach has now been applied to the study of facial emotion processing in a wide range of neuroscience applications.

A large volume of neuroscientific work has focussed on understanding how facial emotions are perceived and processed by the brain, employing techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). The mPFC is commonly found to be activated in response to emotion in general, leading to the assumption that this area plays a role in most aspects of emotion processing (Phan et al 2002). This is supported by analysis of face processing compared to scene processing, a meta-analysis of which found that the mPFC, as well as the amygdala, was repeatedly activated when viewing emotional scenes as well as emotional faces in neuroimaging studies (Sabatinelli et al 2011). However, when emotion processing in general is compared to the processing of specific facial emotions, it becomes clear that there are specialised brain regions responsible for processing distinct facial emotions. This is demonstrated in a meta-analysis of 105 MRI studies of emotion, in which Fusar-Poli and colleagues (2009) found that distinct brain

areas were consistently activated in response to each of the facial expressions happiness, sadness, anger, fear, disgust, and to neutral faces (table 1.2). Of all the brain areas activated in response to facial emotions, both the amygdala and insula seem to be particularly specialised in the processing of specific emotions.

Processing of facial emotions

Facial expression	Brain regions activated
Neutral	visual areas (bliateral fusiform gyrus, left lingual gyrus, inferior occipital gyrus)
	cerebellum
	limbic areas (left amygdala, left cingulate gyrus)
	subcortical areas (right lentiform nucleus)
	prefrontal regions (left medial frontal gyrus, right middle frontal gyrus, precentral gyrus)
	left unsula
Happy	right middle occipital gyrus
	left precuneus
	left amygdala
	left insula
	left medial frontal gyrus
	left putamen
	left cerebellum
	bilateral supramarginal gyrus
	left middle temporal gyrus
Sad	right superior occipital gyrus
	left insula
	left thalamus
Angry	right and anterior cingulate gyri
	right parahippocampal gyrus
	left cerebellum
	subcortical regions (bilateral inferior frontal gyrus, right middle frontal gyrus)
Fearful	bilateral amygdala
	fusiform gyrus
	right cerebellum
	left inferior parietal lobe
	left inferior frontal gyrus
	right medial fontal gyrus
Disgusted	left amygdala
	fusiform gyrus
	bilateral middle temporal gyrus

left middle frontal gyrus
right inferior frontal gyrus
right insula
left precentral gyrus
left inferior parietal lobule
left thalamus

Table 1.2. Results from Fusar-Poli meta-analysis showing brain areas activated higher than baseline in response to each facial emotion.

The amygdala and fear

The amygdala appears to play a key role in emotion processing in general, and has been described as the "gateway to the emotions" (Aggleton and Mishkin 1986). In a number of studies, the amygdala consistently displays increased activation in response to a range of emotional faces compared to neutral faces (Todorov 2012, Fusar-Poli et al 2009, Habel et al 2007). Amygdala activation to emotion is also evident regardless of attention, showing increased activation to both implicit and explicit facial emotion (Habel et al 2007), and further highlighting the importance of the amygdala in facial emotion recognition.

However, the amygdala is best known for its role in fear conditioning and threat detection (Adolphs 2008, LeDoux 1998) and it does appear to be the case that greatest activation in the amygdala is evident in response to fearful faces (Adolphs 2008, Phan et al 2002, Buchel and Dolan 2000, Morris et al 1996). For example, happy, sad and fearful faces were all shown to increase activation in the amygdala, but the greatest increase in activation was noted in response to fearful faces, suggesting increased sensitivity of the amygdala to the emotion of fear (Fusar-Poli 2009). The selectivity of the amygdala in fear processing can be

further illustrated by studies of an individual with Urbach-Wiethe disease, which causes calcification bilaterally of the medial temporal lobes, particularly the amygdalae. It was found that this person was unable to recognise fearful faces, while recognition of other emotions remained unimpaired (Adolphs et al 1994).

The insula and disgust

Although there is evidence that the insula is involved to a lesser extent in the processing of fear, it appears to be specialised in the recognition, experience and processing of disgust (Jabbi et al 2008, Sprengelmeyer et al 1998, Phillips et al 1997). Fusar-Poli and colleagues (2009) found that, while the insula was activated by both fear and disgust, activation was far higher in this region when viewing disgusted compared to fearful facial expressions. It has also been reported that the insula is only activated in response to fearful faces when stimuli are attended to fully by participants, however increased insular activation has been noted in response to disgusted faces, even when attention was divided (Chapman and Anderson 2012). Lesion studies have also provided compelling evidence for the selectivity of the insula in disgust recognition. One patient with bilateral insular lesions was unable to recognise disgust in any context, but remained able to recognise all of the other primary emotions (Adolphs et al 2003), and studies of Huntington disease patients with insula damage have showed impaired recognition of disgust (Ibanez et al 2010, Sprengelmeyer 2007).

1.2.2. Social cognition

Effective social interaction requires the involvement of a network of brain areas, including the integration of regions involved in face processing, as described above (figure), in order to gather, retrieve and process relevant information in the correct way. Such interaction is fundamental not just in cultivating and maintaining relationships with others, but for everyday functioning and social interaction of all kinds. In order to successfully facilitate this process, human beings must have an intrinsic understanding not just of their own emotional state and intentions, but also those of the people around them (Lieberman 2007). The process of attaining and utilising such information is commonly known as social cognition.

Two processes imperative for functional social cognition are theory of mind (ToM), or mentalising, and empathy. Theory of mind is the ability to attribute mental states to others in social situations, and to have insight into the intentions of other people, based on the understanding that they will have their own beliefs and desires. Empathy, on the other hand, is the process of inferring the emotional states of others, achieved by creating an affective state in oneself to mimic and understand the affective state of another person (for review see Frith and Singer 2008).

Several brain areas are known to be involved in social cognition. For example, the fusiform gyrus and superior temporal gyrus are implicated in the processing of facial features and face recognition (Iidaka 2014). Similarly, the Default Mode Network (DMN) - a network of brain areas, including the medial temporal lobe (MTL), medial frontal cortex (MPFC), cingulate cortex and precuneus, that is active during wakeful rest, is commonly reported as active during social cognition tasks (Li et al 2014, Mars et al 2012). However, social cognition is complex, and involves a multitude of neural processes that cannot be confined to just one or two networks. Most of the brain regions that are important for emotion processing are also relevant in social cognition, and different areas seem to be responsible for specific aspects of processing.

The MTL, which includes the amygdala and hippocampus, is involved in emotional processing, emotional memory, and the retrieval of a range of socially relevant information (Somerville et al 2006). The MTL, though, can be further subdivided to reveal even greater specificity of neural processes in social cognition. The amygdala is involved in motivational evaluation, and has reciprocal connections with the orbitofrontal cortex (OFC) and ventral striatum. These areas are believed to compose a neural system responsible for linking environmental stimuli with the social judgements we make about people (Adolphs 2003). For example, the amygdala is commonly found to be activated in studies of race (Kubota et al 2012). The amygdala is also activated in response to untrustworthy faces, with activation increasing with increasing

untrustworthiness (Winston et al 2002); and the OFC (O'Doherty et al 2003) and ventral striatum (Aharon et al 2001) have been shown to be activated in response to attractive faces.

The MPFC is believed to have a role in self-knowledge and in processing emotionally or socially relevant information about others (Shurz et al 2014, Amodio and Frith 2006). The MPFC, along with the cingulate cortex are activated during decision-making tasks involving inference of the intention of and awareness of the behaviour of others (Ruff and Fehr 2014, Tomlin et al 2013, Stanfey et al 2003). The subjective experience of emotion and pain has also been shown to activate the MPFC, while the cingulate cortex appears to be activated in response to painful and unpleasant stimuli more generally (Amodio and Frith 2006). Finally, the role of the precuneus is believed to be in mental visualisation (Shurz et al 2014). It appears then, that different areas of the brain are recruited to differential degrees depending on the cognitive process required, the type of stimuli presented, and the context in which those stimuli appear.

1.2.3. Facial emotion recognition in BPD

Emotion dysregulation is a core clinical feature of BPD (see chapter 1), and has an effect on both personal experience of emotion and emotion recognition. It is believed that the emotion dysregulation so commonly displayed in those with a

diagnosis of BPD is caused by heightened sensitivity to emotions, and a substantial body of work has investigated this.

Behavioural studies of facial emotion recognition in BPD

Meta-analysis of ten behavioural studies that employed facial emotion recognition tasks (Daros et al 2013) found that recognition of the six basic emotions (anger, disgust, fear, happiness, sadness, surprise) was impaired in those with a diagnosis of BPD. Studies have also reported that negative facial emotions (anger, disgust, fear, sadness) are recognised least accurately in BPD (Unoka et al 2007), with Bland et al (2004) finding least accurate recognition of anger, fear and sadness, and Levine et al (1997) showing least accuracy in recognition of anger, disgust and fear. All of these studies used stimuli taken from the Pictures of Facial Affect (PFA) (Ekman and Friesen 1976). Daros and colleagues' meta-analysis found that disgust was correctly recognised least often in BPD. Furthermore, individuals with a diagnosis of BPD have been found to frequently misattribute disgust to other facial emotions (Unoka et al 2007), further highlighting sufferers' difficulties with this emotion. It has also been commonly reported that those with a diagnosis of BPD have a tendency to classify neutral or ambiguous facial expressions as negative (Mitchell et al 2014, Domes et al 2009, Dyck et al 2009, Wagner and Linehan 1999). This finding supports the notion that individuals with a diagnosis of BPD tend to view their surroundings and others more negatively than do the healthy population (Giessen-Bloo and Arntz 2005). The findings from these studies provide

compelling evidence that emotion recognition is impaired in those with BPD, and that processing and attributing negative emotions is particularly inaccurate in this group.

However, not all studies of facial emotion recognition in BPD have yielded similar results. Dyck et al 2009 utilised the Emotion Recognition (ER) test in a group of individuals with BPD and a group of healthy controls, and found no significant difference in emotion recognition between the two groups. The difference in findings between this task and those mentioned above may be attributed to task differences, as the ER includes only four emotions – happiness, sadness, fear and anger – and stimuli were not taken from the PFA. Participants also had no time limit during which a decision had to be made. Again, this is different from studies using stimuli from the PFA, as in these studies faces were displayed on screen for a limited and distinct length of time. It may be the case that those suffering from BPD are capable of accurately identifying facial emotions, but may require more time in order to do so. Indeed, the same study found that the BPD group was less well able to correctly identify facial emotions compared to controls in the Fear Anger Neutral (FAN) test, which requires rapid discrimination between and labelling of these three facial expressions.

Task differences, though, cannot be solely responsible for the inconsistent results reported in studies of facial emotion recognition in BPD. One study that did use stimuli from the PFA found no significant difference in performance

between BPD and healthy control groups (Minzenberg et al 2006), despite employing similar methods to studies that did report group differences. Similarly, Robin et al (2012), Lynch et al (2009) and Domes et al (2008) all investigated emotion recognition using extremely similar methods, but produced differing conclusions. All three studies utilised stimuli from the PFA, which morphed from neutral to emotional expressions. Participants were required to indicate when they first noticed the appearance of an emotion, and what they thought that emotion was. While Robin et al (2012) and Domes et al (2008) reported no difference in performance between those with BPD and healthy controls, Lynch et al (2009) found that those with BPD were able to identify emotions more quickly than controls, indicating a heightened sensitivity in this group to emotion. Other factors that may contribute to the varying results must therefore be considered. All three studies used similarly small sample sizes of approximately 20 per group, and groups were well matched; however the mean age was quite different in each (16.9 in Robin, 26.0 in Domes, 35.5 in Lynch). Each group also collected different clinical and demographic information from participants, so comorbidity, symptom severity, BPD criteria met cannot be compared between the three, and each of these could be responsible for some of the variation in task performance.

The idea of heightened sensitivity to emotion in BPD has also been suggested by Shulze et al (2013), who found that individuals with this diagnosis were better able to detect an emotional face in a stream of facial stimuli, compared to healthy control participants. However, in this study, participants did not have to

identify specific emotions, merely the appearance of an emotional face (as opposed to a neutral face).

Given the variation in results, it is difficult to draw any definite conclusions about facial emotion recognition in BPD from behavioural studies alone. While it does appear that individuals with a diagnosis of BPD do differ from the healthy population in their processing and recognition of emotions, the particular deficits remain unclear. In addition, the heterogeneity of results concerning emotion recognition in BPD cannot be accounted for based on the current literature. It is possible that aetiological factors, such as childhood trauma, may contribute, but this has yet to be systematically studied.

Functional MRI studies of facial emotion processing in BPD

FMRI studies of facial emotion recognition commonly report activation differences in the amygdala between those with BPD and healthy controls (Mitchell et al 2014, Mier et al 2013, Guitart-Masip et al 2009, Minzenberg et al 2007, Donegan et al 2003), despite the use of different tasks.

Two studies involved an implicit recognition task, in which there was no mention of emotion to participants. Donegan et al (2003) required participants to attend to photographs of faces only, with no "task" as such to be carried out. The faces shown displayed neutral, happy, sad or fearful expressions, and

results showed increased activation in the left amygdala in the BPD group versus controls in response to facial expressions compared to a fixation point. MInxenberg et al (2007) asked participants to view photographs of emotional faces (neutral, fearful, angry), and to select whether each face was male or female. This group also noted an exaggerated amygdala response compared to controls, which showed hyperactivation in response to fearful faces, but hypoactivation in response to angry faces.

In an explicit emotion study, participants were shown a statement on screen, which was followed by an emotional face, for example "this person is angry". Participants then had to select yes, if they thought the statement and face agreed, or no if not (Mier et al 2013). Again, this task yielded hyperactivation in the amygdala in those with BPD compared to controls, despite the lack of any behavioural differences between groups. Guitart-Masip et al (2009) also utilised an explicit emotion study, in which participants were shown two faces and had to select which of the two was showing emotion. This task was shown to activate the amygdala, fusiform face area and insula and, additionally, those with BPD displayed greater activation in the middle and inferior temporal cortical areas compared to healthy controls. This study also found that the BPD group made more errors when negative emotional faces were shown, which is in keeping with some of the behavioural evidence of facial emotion processing in BPD.

Increased amygdala activation in response to facial emotion is in keeping with other studies of emotion processing in BPD, which used emotionally arousing pictures of objects or scenes, but not faces. Such studies consistently reported increased amygdala activation when presented with emotionally arousing images compared to neutral images or a rest condition (Hazlett et al 2012, Koenigsberg et al 2009, Herpertz et al 2001).

Overall, the results of facial emotion processing studies in BPD do point to some abnormality of function in those suffering from the disorder, particularly in the amygdala. While these findings provide some insight into the disorder, the relationship between behavioural and particularly neural abnormalities in BPD and developmental experience has not been extensively investigated. More work needs to be done in order to obtain a more complete understanding of BPD and its aetiology.

1.2.4. Social cognition in BPD

Difficulties in emotion processing in BPD are likely to contribute to the social difficulties experienced by those suffering from the disorder; however we gather a great deal more information from the people around us than just emotional facial expressions (see chapter 1). Studies of social cognition investigate responses to people and social situations, requiring an understanding of others' thoughts, feelings or intentions. Several have been

carried out in BPD populations to try to better understand the social-cognitive deficits that so commonly affect those with the disorder.

Behavioural studies of social cognition in BPD

A common test of social cognition is the Reading the Mind in the Eyes Task (RME), which involves participants viewing photographs of the eye region of the face only, and attempting to infer the mental state of each person. The RME has been used several times in studies with BPD populations, but with varying results. Baez et al (2014) and Preissler et al (2010) reported no group differences in performance, while Fertuck et al (2009) found that those with BPD performed better than controls, and Scott et al (2011) noted that those with BPD performed better than controls when detecting negative mental states, but not neutral or positive. However, Scott et al (2011) also found that the BPD group was more likely to attribute negative emotions to all stimuli, so it may be that the improved scores for negative stimuli is due to a negativity bias, and not improved accuracy per se.

Lack of performance differences between those with BPD and controls has also been reported on the MSAT-S and MSAT-Q, which assess mentalising ability (Ghiassi et al 2010). The MSAT-S requires participants to order sections of a carton strip in the correct order to create a story, and the MSAT-Q asks questions regarding the mental state of the characters included. In addition, no

group differences were found between groups in a task involving attributing mental states to static photographs of faces (Mier et al 2013).

Group differences have been reported in the Faux Pas Test (FPT), in which participants are asked to identify a social faux pas within a story. Control participants appear better able to identify a faux pas in this task than those with a diagnosis of BPD (Baez et al 2014, Harari et al 2010). Significant differences in performance between groups was also noted in a study by Preissler et al (2010) which employed the Movie for the Assessment of Social Cognition (MASC). This group found that people with a diagnosis of BPD were less well able to attribute mental states to characters in films of everyday situations than were control participants.

From the previous studies of social cognition in BPD, it appears that the type of task used has an effect on participant performance. For example Harari et al (2010) found reduced performance on cognitive empathy, but not affective empathy tasks in a BPD population. It may also be that tasks that closely resemble real-life situations are processed differently to more artificial situations, accounting for differences in results between studies.

In addition, two research groups, which included a measure of previous experience in their study procedure, found correlations between negative experiences and social cognitive task performance. Ghiassi et al (2010) found that individuals who had been separated from a parent at an early age were

impaired in their mentalising ability. Preissler et al (2010) also found that individuals in the BPD group who had experienced sexual abuse were less well able to correctly identify mental states in the MASC, again suggesting a deficit in mentalising ability. It therefore appears that not purely diagnosis, but traumatic childhood events can have an effect on social cognition; however few studies thus far have investigated this idea in depth.

1.3. Study design

The following work includes information and data from two studies comprising the Edinburgh Emotional Symptoms Study (EESS). The first, pilot study involved individuals with a diagnosis of BPD, as well as matched controls, completing a full clinical assessment and a number of neuropsychological tests, as detailed in chapter 2. The second, main study replicated the pilot study in terms of clinical assessment and neuropsychological testing, but with the addition of both the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) and the positive component of the Positive and Negative Syndrome Scale (PANSS). These two items were included in the clinical assessment in order to gain as much information as possible about the type and severity of symptoms experienced by individuals in the BPD group. The main study also included an MRI brain scan, lasting approximately one hour, which comprised both structural and functional imaging sequences. Studies were separated by approximately one year, and approximately 40% of those with a diagnosis of

BPD who took part in the imaging study had previously completed the pilot study (figure 1.2).

Figure 1.2. EESS pilot and main study organisation

Participants with a diagnosis of BPD were recruited from outpatient populations in Edinburgh and The Lothians by Merrick Pope (Royal Edinburgh Hospital, Edinburgh), Professor Jeremy Hall (The University of Edinburgh, Edinburgh) and Dr Prakash Shankar (St John's Hospital, Livingston). Control participants were recruited from the community by Merrick Pope, Professor Jeremy Hall and Katie Nicol. All participants were informed verbally about the study, before being given detailed information sheets to review before agreeing to take part. Following verbal consent, appointment details were mutually agreed, and written consent was obtained following another briefing of the study, with the opportunity to ask questions and discuss any points.

All clinical assessments were carried out by Professor Jeremy Hall, with Katie Nicol present (main study only). Pilot study behavioural testing was carried out by Merrick Pope, and the main study behavioural testing was carried out by Katie Nicol. In the main study, scanning sequences were overseen and MRI tasks run by Katie Nicol. Pilot study analysis was completed by Professor Jeremy Hall,

Merrick Pope and Katie Nicol, while data from the main study (clinical, behavioural and imaging) was completed by Katie Nicol (see table 1.3).

Pilot Study			
Recruitment	Clinical assessment	Behavioural data collection	Data analysis
Merrick Pope Jeremy Hall	Jeremy Hall	Merrick Pope	Merrick Pope Jeremy Hall Katie Nicol
Main Study			
Recruitment	Clinical assessment	Behavioural/imaging data collection	Data analysis
Merrick Pope Jeremy Hall Katie Nicol	Jeremy Hall	Katie Nicol	Katie Nicol

Table 1.3. EESS pilot and main study – details of division of responsibilities.

1.4. Aims and hypotheses

In the following work, we aim to develop a better understanding of the aetiology and neurobiological underpinnings of BPD. In particular, we aim to investigate the effects of childhood adversity, as measured by the CTQ, on common symptoms and behaviour associated with the disorder. The following work represents a novel approach to research into BPD and, by investigating any existing correlations between these measures, we hope to expand upon the current knowledge and theories regarding BPD. We aim to report not only

defects present within the disorder, but to provide potential links and explanations as to why such defects and difficulties may occur. To achieve these goals, the study and thesis will include the following:

1. Neuropsychological testing of those with a diagnosis of BPD and a group of matched healthy control participants (pilot study). Specifically, tests of social judgement and emotion recognition were utilised to reflect the common, disabling symptoms of the disorder, such as emotion dysregulation and defective social cognition. Clinical measures were also recorded for correlation analysis, in order to investigate the relationship between clinical and behavioural measures of BPD. We expect that individuals with BPD will perform less well than controls in tasks of both social judgement and emotion identification, and that performance will correlate with clinical measures of the disorder, in particular the CTQ.

2. Analysis of the brain structure, in particular grey matter volume, of those with a diagnosis of BPD and a group of matched healthy control participants (main study). Structural MRI data was collected for each participant, along with clinical measures for correlation analysis, to investigate the relationship between brain structure and the common symptoms and behaviours associated with BPD. We expect to find differences in grey matter volume between groups, in particular in regions known to be key to social cognition, such as the amygdala and hippocampus. More specifically, we expect that reductions in grey matter volumes in these areas are likely in those with a diagnosis of BPD

compared to control participants, based on existing structural imaging studies of the disorder. In addition, we expect any structural abnormalities in BPD to be related to clinical measures of the disorder, particularly the CTQ.

3. Analysis of brain function of those with BPD and healthy controls using fMRI data (main study). Functional activation in response to emotional facial stimuli was recorded during MRI scanning, along with clinical measures out with the scanner for correlation analysis, in order to investigate the relationship between brain function and clinical symptoms of BPD. We expect brain function to differ between groups, particularly in the amygdala, based on previous research into BPD. We also expect that functional abnormalities in BPD will be related to clinical measures of the disorder.

4. Analysis of functional connectivity in the three major networks – CEN, SN and DMN – in those with a diagnosis of BPD and matched healthy controls. We used data from our functional imaging sequences in order to identify these three networks and any associated abnormalities. In keeping with previous functional connectivity studies of BPD, we expect to find altered functional connectivity in all three networks in those with BPD compared to controls. We also expect that amygdala connectivity may be particularly altered in the disorder.

2. General Methods

2.1. Recruitment

Participants with a diagnosis of BPD were recruited from outpatient populations, either by their clinical psychiatrist or specialist nurse. Matched control participants were recruited from the wider community by word of mouth and included hospital staff, university staff, students, friends of participants etc.

Participants were informed verbally about the study, and if interest was expressed, they were given a detailed study information sheet, which included contact details to discuss any queries. Potential participants were re-contacted within a week, and verbal consent to take part was obtained, as well as a suitable appointment time. A short discussion about the study, as well as an opportunity to ask questions was included at the start of each appointment, before written consent was obtained.

2.2A. Participant inclusion and exclusion criteria – Pilot study

Healthy control group

Healthy control participants were males and females recruited from the community. All were aged between 18 and 52 years, reported no history of neurological disorders (epilepsy, seizures), were free from psychiatric illness and had normal, or corrected to normal vision.

BPD group

Participants were males and females recruited from outpatient populations. All were aged between 18 and 52 years, with a diagnosis of borderline personality disorder. Diagnosis of BPD was confirmed by a clinician at study commencement. Exclusion criteria included any neurological illness, history of bipolar I disorder, schizophrenia or other axis I psychiatric condition, and drug or alcohol dependency at the time of study. Participants were of normal intelligence as determined by the National Adult Reading Test (NART). All individuals were able to read and understand the participant information sheet, ask questions and provide informed written consent.

2.2B. Participant inclusion and exclusion criteria – Main study

Healthy control group

Healthy control participants were males and females recruited from the community. All were aged between 18 and 53 years, reported no history of neurological disorders (epilepsy, seizures), were free from psychiatric illness

and had normal, or corrected to normal vision. Participants completed the Clinical Research Imaging Centre (CRIC) Edinburgh MRI screening form. Individuals were included in the sample who were not pregnant, were free from metal implants or prostheses (eg pacemaker, vascular surgery clips, metallic stents, surgical staples, cochlear implant), as well as any metallic fragments or foreign bodies, and had no piercings, braces, dentures or make-up which could not be removed. All participants provided written informed consent to take part in the study.

BPD group

Participants were males and females recruited from outpatient populations. All were aged between 18 and 53 years, with a diagnosis of borderline personality disorder. Diagnosis of BPD was confirmed by a clinician at study commencement. Exclusion criteria included any neurological illness, history of bipolar I disorder, schizophrenia or other axis I psychiatric condition, and drug or alcohol dependency at the time of study. Participants were of normal intelligence as determined by the National Adult Reading Test (NART). All individuals were able to read and understand the participant information sheet, ask questions and provide informed written consent. Participants also completed the CRIC MRI screening form to ensure safety in the scanner.

2.3. Demographics

All participants were asked to provide basic demographic information regarding age, sex, handedness, level of education. This information was used to match the healthy control and BPD groups. Participants also provided information about current medication where applicable.

2.3A Demographics - Pilot study

Twenty participants meeting DSM-IV criteria for borderline personality disorder and 20 matched healthy controls were recruited for the study (table 2. The BPD group consisted of 15 females and 5 males, mean age 34.3 years (SD 8.5) and mean IQ 115.9 (SD 7.4), assessed by the NART. Of these, 11 were being treated with antipsychotic medication, and 13 were being treated with antidepressant medication. Fourteen participants had comorbid diagnoses at the time of study, including bipolar affective disorder ii, eating disorders, PTSD and OCD. Three participants each had two comorbid diagnoses. The control group consisted of 16 females and 5 males, mean age 34.5 years (SD 11.6) and mean IQ 114.2 (SD 7.3).

	BPD			Healthy control		
Demographics	n	mean	SD	n	mean	SD
Age	20	34.3	8.5	21	34.5	11.6
IQ	20	115.9	7.4	21	114.2	7.3
CTQ	20	37.4	17.6	21	1.2	1.7
HAM-D	20	14.5	8.3	21	0	0
YMRS	20	2.5	2.4	21	0	0
Number of BPD criteria (max 9)	20	7.4	1.3	21	0	0
Medication	n	%				
Antipsychotic medication	11	55				
Antidepressant medication	13	65				
Comorbid diagnoses	n	%				
Total	14	70				
Bipolar affective disorder ii	4	20				
Eating disorder	6	30				
PTSD	2	10				
OCD	2	10				
Other	3	15				

Table 2.1. Pilot study demographics

2.3B. Demographics – Main study

Twenty individuals with a diagnosis of BPD and 16 matched healthy controls were recruited for the study. DSM-IV criteria for a diagnosis of BPD were established using the SCID-II. The BPD group consisted of 17 females and 3 males, mean age 35.8 (SD 8.6) and mean IQ 114.8 (SD 7.9), assessed by the

NART. Of these, 12 were being treated with antipsychotic medication, and 15 with antidepressant medication. Seventeen participants had comorbid diagnoses at the time of study, including depression, bipolar affective disorder ii, eating disorders, PTSD, OCD. The healthy control group comprised 14 females and 2 males, mean age 34.8 (SD 9.6) and mean IQ 114.5 (SD 6.0).

	BPD			Healthy control		
Demographics	n	mean	SD	n	mean	SD
Age	20	35.8	8.6	16	34.8	9.6
IQ	20	114.8	7.9	16	114.5	6
CTQ	20	52.9	19.8	16	13.1	11.5
HAM-D	20	15.5	8.6	16	0	0
YMRS	20	2.1	3.1	16	0	0
PANSS above baseline	20	2.6	2.5	16	0	0
ZAN-BPD	20	13.7	6.7	16	0	0
Medication	n	%				
Antipsychotic medication	12	60				
Antidepressant medication	15	75				
Comorbid diagnoses	n	%				
Total	17	85				
Depression	4	20				
Bipolar affective disorder ii	4	20				
Eating disorder	3	15				
PTSD	2	10				
OCD	2	10				
Other	2	10				

Table 2.2. Main study demographics

2.4. Ethics

Studies and experiments were approved by the Lothian Research Ethics Committee. All participants gave written informed consent following a period of at least 24 hours consideration with access to the study information sheet. All participants had the opportunity to discuss the study and ask questions, and understood that they were free to withdraw at any time. Participants who withdrew from the study were not disadvantaged in any way.

2.5. Clinical interview

All participants were clinically interviewed by a trained psychiatrist.

The Hamilton Rating Scale for Depression (HAM-D)

The Hamilton Rating Scale for Depression (HAM-D) was developed by Hamilton (1960). It consists of 17 variables, which are marked on either a three point or five point scale to measure symptom frequency and intensity. The three point scale is used when more discrete quantification of the variable is difficult or not possible. In addition to these 17, there are a further four variables included on

the rating form, however these are either very rare symptoms of depression, or exist to define the type of depression.

In total, the 21 items of the HAM-D cover depressed mood, feelings of guilt, suicide, sleeping pattern, work and loss of interest, retardation, agitation, anxiety, eating and weight loss, somatic symptoms, insight.

The Positive and Negative Syndrome Scale (PANSS) – Main study only

The Positive and Negative Syndrome Scale (PANSS) was developed as a standardised instrument to measure both the positive and negative symptoms frequently experienced by those suffering from schizophrenia, in order to give an accurate overview of symptomology and difficulties (Kay et al 1987).

Here, participants were asked questions from the positive scale only, which consists of 7 items (P1-P7) covering delusions, conceptual disorganisation, hallucinatory behaviour, excitement, grandiosity, suspiciousness/persecution, hostility.

The Young Mania Rating Scale (YMRS)

The Young Mania Rating Scale (YMRS) is used to assess the severity of symptoms of mania. The YMRS contains 11 items, each of which is scored on a five point scale. The severity of each item is scored based on the participant's self-report of their symptoms over the past 48 hours, as well as observed behaviour during interview (Young et al 1978). The 11 items included in the YMRS are elevated mood, increased motor activity-energy, sexual interest, sleep, irritability, speech, language-thought disorder, content, disruptive-aggressive behaviour, appearance, insight.

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) is used to determine Axis-1 psychiatric disorders, for example schizophrenia, bipolar I disorder, major depressive disorder. The SCID-I is split into six modules, and covers recent symptoms, as well as past symptomology.

The Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)

The Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) is used to determine Axis II personality disorders (First et al 1997). The SCID-II semi-structured clinical interview was used in conjunction with the SCID-II questionnaire, which participants completed prior to interview. The 119 item questionnaire covers all personality disorders, with each question requiring a "yes" or "no" response and corresponding to a question in the SCID-II interview. Only questions to which the respondent has answered "yes" need to be asked in further detail during the interview. Since the SCID-II acts as a screening device, it is likely that there will be several false positives, so the interviewer must cover these items in more detail to ascertain whether or not an answer of "yes" can really be given. Items 90-104 in the SCID-II relate to borderline personality disorder.

The Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) – Main study only

The Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) was developed by Zanarini (2003) in order to quantify the symptoms of BPD experienced during the week preceding interview. The 9 items of the ZAN-BPD reflect the nine criteria on which a diagnosis of BPD can be made, as listed below, and each item is rated on a five point scale.

1. Inappropriate, intense anger, or difficulty controlling anger

2. Affective instability due to marked reactivity of mood

3. Chronic feelings of emptiness

4. Identity disturbance: markedly and persistently unstable self-image or sense of self

5. Transient stress-related paranoid ideation or severe dissociative symptoms

6. Frantic efforts to avoid real or imagined abandonment

7. Current suicidal behaviour, gestures or threats, or self-mutilating behaviour

8. Impulsivity in at least two other areas that are potentially self-damaging

9. Pattern of unstable and intense interpersonal relationships characterised by alternating between extremes of idealisation and devaluation

2.6. Questionnaires

Childhood Trauma Questionnaire (CTQ)

The Childhood Trauma Questionnaire (CTQ) is a self-report measure of adverse events in childhood (appendix 1). The CTQ has 28 items and quantifies the severity of five different types of trauma – emotional neglect, physical neglect, emotional abuse, physical abuse and sexual abuse. For each question, participants were asked to select from one of five possible responses – never true, rarely true, sometimes true, often true, very often true. Of the 28 questions, 18 relate to one of the five subscales, while the remaining 10 do not relate to

any specific type of abuse or neglect. For some analyses, the CTQ questions and scores were separated into the five subscales (table 2.3).

Subscale	Question number
Emotional neglect	8, 18
Physical neglect	1, 4, 6
Emotional abuse	3, 14, 25
Physical abuse	9, 11, 12, 15, 17
Sexual abuse	20, 21, 23, 24, 27

Table 2.3. Table showing the five subscales of the CTQ and the questions relating to them.

2.7. Neuropsychological testing

The National Adult Reading Test (NART)

The National Adult Reading Test (NART) is a method for estimating premorbid IQ in participants for whose first language is English (Nelson 1982). The NART comprises a list of 50 words, which participants are asked to read aloud. The

number of incorrect pronunciations is recorded and can be used to estimate premorbid intelligence.

Ekman 60 Faces Test

Participants completed the Ekman 60 Faces Test (Young et al 2002, Ekman and Friesen 1976), in which one of six emotions was identified from each photograph in a series of 60 faces depicting one of anger, disgust, fear, happiness, sadness or surprise. The series of 60 photographs consisted of ten actors, five male and five female, all depicting each of the six emotions. Faces appeared on a computer screen for 3 seconds each, in a randomised order. The names of all six emotions were listed on the screen, and subjects made a selection by clicking the mouse over the desired name. The next face was not shown until a selection had been made. Participants were shown six practice images, covering the six emotions, which were not included in analysis. An equal number of faces was shown for each emotion, and responses were recorded on the computer, with no feedback provided throughout the task.

A score out of ten was awarded for each of the six emotions – one point for each correct answer – which was used in analysis to determine deficits in emotion recognition.

Test of social judgement from faces

Participants completed a test of social judgement from faces involving six blocks of trials in which participants judged whether each of a set of 32 photographs of faces was 'high' or 'low' on a specified characteristic (Santos and Young 2008, Hall et al 2004). The characteristics to be judged in each block of trials were age, distinctiveness, attractiveness, intelligence, approachability and trustworthiness.

Only a single characteristic was judged in each block of 32 trials. Faces appeared on a computer screen for 3 seconds each and participants were asked to choose from two options for the judged characteristic (eg “trustworthy” or “untrustworthy”). Judgements were reported verbally to the experimenter, and there was no limit on how long participants were given to make a choice, but the next picture was not shown until a judgement had been made. Answers were recorded by the experimenter but no feedback was provided. Participants judged 8 practice images before each block of trials; these were not included in the analysis.

The images used for each judgement were based on ratings of a set of 500 images of faces taken from the internet. From these 500 rated images, 16 that were rated high and 16 rated low on a given characteristic were chosen to create the set of images used to test perception of that characteristic, in such a

way that each of the selected sets of high and low images for a particular characteristic were matched as closely as possible across the other five characteristics (Santos and Young 2008, Hall et al 2004).

The total number of correct and incorrect judgements for each of the six characteristics was recorded for each participant, as well as the direction of decision bias – for example trustworthy faces being judged as untrustworthy, or vice versa. Note that the sense in which a judgement is considered correct is simply that it is in agreement with the set of ratings from which the faces were chosen (that is, a highly rated face judged as 'high' is considered a correct judgement, and a low rated face judged as 'low' is likewise considered a correct judgement).

For each of the six characteristics tested (intelligence, distinctiveness etc), a score out of 32 was given (one point for each correct answer), which was used in analysis to identify deficits in social judgement. Where an incorrect answer was given, the direction of the error, either positive or negative (positive being eg untrustworthy judged as trustworthy and negative being eg trustworthy judged as untrustworthy) was also recorded. The number of each type of error was used in analysis to determine judgement bias.

2.8. Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) is a technique used to create detailed images of internal tissues and structures, in this case the brain, using a strong magnetic field and radio waves. The majority of scanners in use for clinical and research use are either 1.5 tesla (T) or 3T, referring to the strength of the magnetic field created by the magnet. Generally, the greater the field strength, the higher the signal-to-noise ratio, resulting in more detailed and accurate images. The technique of MR imaging depends on the protons present in the water molecules within our bodies, which align with the strong magnetic field in the MRI scanner (longitudinal magnetisation). Radio waves, known as RF pulses, are used to change the alignment of these protons, which subsequently absorb energy and return to their original alignment. This process causes a change in signal that is detected by a specially designed radiofrequency coil, which surrounds the head of the participant. The radio waves can be manipulated in order to create contrast between different tissues and build a complete image of the brain (Edelman and Warach 1993).

The contrast of the images acquired can be manipulated, and they may be T1 or T2 weighted. T1 refers to the longitudinal relaxation or recovery time, which is the time taken for the protons in a tissue to once again realign longitudinally following an RF pulse. T2 refers to the transverse relaxation time, which is the length of time protons remain “in phase” following an RF pulse, which is used to tilt the longitudinal magnetisation into the transverse plane (Chavhan et al

2009). T2 relaxation time is dependent on the interaction between atoms and molecules within tissue and the small, local magnetic fields they create; it does not involve the transfer of energy, instead decay occurs due to loss of spin homogeneity between molecules (Mitchell et al 1987). As a result of these different relaxation measures, water appears bright in T1 weighted images, while in T2 images water appears dark (figure 2.1). In brain MR imaging, T1 weighted images tend to be used for anatomical scans, while T2 weighted images are required for use in functional imaging.

Two critical parameters, which can be altered in MR sequences, are echo time (TE) and repetition time (TR). TE is the time lapse between RF excitation and subsequent signal detection, while TR indicates the time between each subsequent RF excitation. Manipulation of these parameters can determine the weighting of the acquired images, and the strength of the signal detected. For example, sequences with short TE and TR will yield T1 weighted images, while long TE and TR produce T2 weighted images (Moser et al 2009).

In the following studies, imaging data was acquired using a 3T Siemens Magnetom Verio Syngo MR scanner, collected at the Clinical Research Imaging Centre (CRIC), University of Edinburgh.

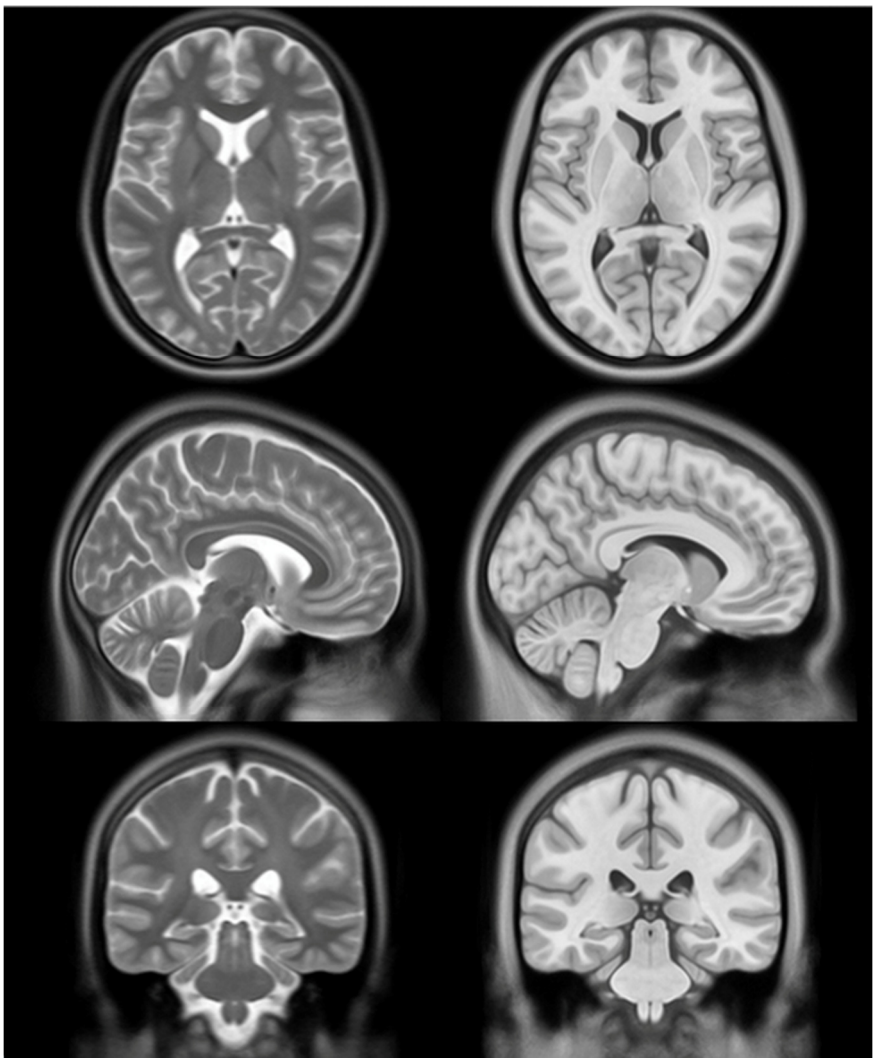


Figure 2.1. Axial, saggital and coronal brain sections demonstrating the difference between T1 weighted (left) and T2 weighted (right) images. Image modified from Lewis Centre for Neuroimaging, University of Oregon website (lcni.uoregon.edu)

2.9. Structural Magnetic Resonance Imaging (sMRI)

Structural Magnetic Resonance Imaging (sMRI) is used to find out information about the shape and size of the brain, and distinguish between grey and white

matter, and other brain structures such as ventricles. Abnormalities in an individual, such as lesions and cysts, can be identified in this way; however in research, brain anatomy between a group of individuals with a specific diagnosis and a group of healthy controls is often compared, in order to identify the pathology or structural anomalies associated with an illness or disease. Voxel based morphometry (VBM) is an analysis technique that is used to compare the volume of grey matter voxel by voxel between groups, in order to identify such differences. This is achieved by spatially normalising the brain images of interest to the same stereotactic space, and separating the grey matter from other brain tissue, known as segmentation. Images are then smoothed, so that each voxel contains the average grey matter volume of its surrounding voxels. Since all brains are different, the normalising step is not flawless, and smoothing helps to compensate for the imprecise nature of this process.

SMRI acquisition

The three-dimension magnetisation-prepared rapid gradient echo sequence (MP-RAGE) is commonly used in clinical and research settings to acquire a whole brain T1 weighted anatomical image. The MP-RAGE sequence provides not only rapid whole-brain coverage, but also produces images with excellent tissue contrast and high spatial resolution, which are widely used in VBM analysis (Wang et al 2014). The MP-RAGE was acquired using the following

parameters: repetition time (TR) 2300 ms, echo time (TE) 2.98 ms, flip angle 9°, slice thickness 1 mm.

SMRI analysis

Data processing was carried out using Statistical Parametric Mapping Software (SPM8, Wellcome Trust Centre for Neuroimaging) and based on MATLAB software version 7.13 (MathWorks).

Analysis was carried out using the VBM- Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra (DARTEL) method, which is described in detail in Ashburner 2007. Briefly, DARTEL involves segmentation of all structural images into grey matter, white matter, CSF, skull and soft tissue outside the brain. This process was carried out using the "new segment" tool in SPM8, and was followed by the creation of a set of study specific templates as follows:

- New Segment – T1 weighted images were selected for segmentation into grey matter, white matter, CSF, skull, tissue outside the brain, and air outside the head.
- DARTEL, create templates – the imported grey matter (rc1*.nii) and white matter (rc2*.nii) images created in the previous step were selected in the same order for the creation of study specific templates.

- Normalise to MNI space – the u_rc1 files created by the previous step were used in order to create spatially normalised grey matter images for use in analysis. Flow fields (u_rc1*.nii) were selected along with the grey matter images (c1*.nii) in the same order.
- Smooth – images were smoothed with a 3-dimensional isotropic Gaussian kernel (8 mm full width at half maximum), ready for use in analysis.

The VBM-DARTEL templates were created using the smoothed images from all study participants. The procedure of creating templates in DARTEL is iterative, with results being updated and a new template created following each iteration, and due to the creation and utilisation of study specific templates, DARTEL has been shown to improve registration and provide more accurate results than other VBM methods in SPM (Li et al 2010, Yassa et al 2009).

In order to investigate any regional between group differences in grey matter volume, contrast images were created for BPD > control and control > BPD. Within group regression analysis was performed across all participants in the BPD group using scores on the PANSS, HAM-D, YMRS and CTQ, with the aim of identifying any existing correlations between grey matter volume and clinical measures/questionnaire scores.

2.10. Functional Magnetic Resonance Imaging (fMRI)

Functional Magnetic Resonance Imaging (fMRI) is a technique used to define and quantify activity within the brain, and uses very fast imaging methods (echo-planar imaging, or EPI) to collect the necessary information. The technique of fMRI is blood oxygen level dependent (BOLD) and relies upon the differences in magnetic susceptibility of oxygenated and de-oxygenated haemoglobin. FMRI does not directly measure neuronal activity, but instead measures changes in the relative levels of oxygenated and de-oxygenated blood. The BOLD technique is believed to be an indirect measure of brain activity since neuronal activity consumes oxygen and increases blood flow. In active brain areas, blood flow increases more than the rate of oxygen consumption, causing the level of oxygenated blood to increase relative to the level of de-oxygenated blood. Deoxygenated haemoglobin is paramagnetic (attracted to the magnetic field) in comparison to brain tissue, and so causes the magnetic field in surrounding tissues to be distorted – as deoxyhaemoglobin decreases, signal increases. Following neural activity, the inhomogeneity of the magnetic field steadily decreases and the magnetic field becomes more homogenous and returns to normal. Since oxygenated haemoglobin is diamagnetic, it is the relative changes in the concentration of deoxygenated haemoglobin that allow a

signal change to be detected and recorded by the MRI scanner (Matthews and Jezzard 2004). This information can then be used to determine areas of increased brain activation during certain tasks.

FMRI task, equipment and acquisition

FMRI tasks were created and presented using Presentation stimulus delivery software run on a Windows PC. Stimuli presented were visual only, with no auditory component, and images were viewed using the NordicNeuroLabs (NNL) visual system. The NNL visual system comprises a set of adjustable eye goggles which attach to the head coil during scanning, allowing the participant to view exactly what is displayed on the stimulus PC monitor.

In the scanner, participants performed a task that involved viewing a photograph of a face on a computer screen, and selecting whether they thought the face was male or female, indicated by pressing the corresponding response button. To ensure that participants had a full understanding of the task, screen-shots of the images used were shown to each person before entering the scanner and a complete explanation of the task was provided. Faces were chosen from the Ekman series of emotional faces (Ekman and Friesen 1976) and displayed either a fearful, disgusted or neutral expression. Faces were not matched for arousal rating. The task was split into two, with one task showing

fearful and neutral faces, and the other showing disgusted and neutral faces. Each task was made up of six blocks, with each block containing six images of faces. Within each block, all of the faces displayed the same emotion –neutral, disgusted or fearful – with half being female and half male, shown in a random order. Faces appeared on the screen for 5 seconds, and a response (male or female) had to be made within this time to be registered, providing a measure of compliance with the task. Selections were made using the NNL response grips, and participants were allowed time to practice using the grips prior to the commencement of scanning. Responses were indicated on the NNL response box and logged by Presentation. Two versions of each task were used, one showing neutral faces in the first block, and the other showing emotional faces (either fearful or disgusted) in the first block. The version of the task shown to each participant was counterbalanced within groups.

Functional imaging scans were acquired using the following parameters: repetition time (TR) 1560 ms, echo time (TE) 26 ms, flip angle 66°, 26 slices (slice thickness 5 mm), field of view (FOV) 220 x 220 mm, voxel size 3.5 x 3.5 x 5 mm.

FMRI analysis

Data processing was carried out using Statistical Parametric Mapping Software (SPM8, Wellcome Trust Centre for Neuroimaging) and run using MATLAB software version 7.13 (MathWorks). The data was reconstructed and examined using the "ArtRepair" toolbox in SPM to assess quality (Mazaika et al 2009). Contrast movies were reviewed and, in the case of particularly noisy data (very bright blue/yellow), bad slice detect and repair was utilised. In this process, bad slices are identified and repaired using data from the previous and following slices. Following the use of ArtRepair on the raw data, the first 6 functional images were discarded, and the remaining images pre-processed as follows:

- Realignment, to correct for motion within each subject. All remaining functional images (f*.img) were selected for realignment, creating plots of the estimated translations and rotations in the time series.
- Coregistration, in which each participant's anatomical scan is registered to their functional data (mean image). The mean functional (meanf*.img) image was selected as the Reference Image, and the structural image (s*.img) was selected as the Source Image. This step improves normalisation to the Montreal Neurological Institute (MNI) brain template, known as standard space.
- Segmentation, to separate the T1 image (s*.img) into white and grey matter. This information is required for normalisation

- Normalisation, in which each subject's data is warped into MNI standard space. The s*_seg_sn.mat file that was created in the segmentation step was selected as the Parameter File. All of the realigned functional images (rf*.img) were selected as Images to Write.
- Smoothing, which averages the intensities of adjacent voxels to account for variability between subjects and improve signal to noise ratio. The normalised files created in the previous step were selected as Images to Smooth, and data was smoothed by 8mm in each direction (8mm FWHM).

3. Emotion recognition and social judgements from faces in BPD

3.1. Introduction

As outlined in chapter 1, individuals with a diagnosis of BPD often have difficulties in emotion regulation and forming and maintaining interpersonal relationships, and such impairments are diagnostic features of the disorder (American Psychiatric Association [*DSM-IV-TR]*, 2000). Gleaning information about others from their facial expressions is an essential component of everyday social encounters, and failure to accurately identify emotional state in this way, as in BPD, contributes to the social difficulties seen in BPD. Misinterpretation of facial expressions and mental state is likely to hinder the development of interpersonal relationships, further preventing efficient social functioning (Unoka et al 2011). These difficulties in social interaction in BPD can make maintaining a job or achieving sustained success in the workplace or in education challenging.

Impaired ability of patients to recognise facial emotions is a frequent finding in studies of BPD (Unoka et al 2009, Merkl et al 2009, Guitart-Masip 2009, Minzenberg et al 2006, Bland et al 2004), with patients displaying a lower rate of emotion recognition than healthy controls, particularly with regard to

negative emotions. A meta-analysis of facial emotion recognition in BPD (Domes et al 2010) compared ten studies, all of which included a task that involved assigning an emotion to pictures of faces. Domes and colleagues found that those with BPD were significantly less accurate in their recognition of facial emotions, and in particular disgust. There was also a significant difference between groups in the recognition of neutral faces, with those in the BPD group misattributing emotions to neutral expressions.

Brain areas known to be involved in emotion processing, including the amygdala and hippocampus (Hall et al 2010b, Ishai et al 2005), have been found to have a reduced volume in patients compared to controls (Nunes et al 2009) and functional MRI studies have also highlighted areas of altered activation in the insular cortex in those with the disorder (Dziobek et al 2011, Niedtfeld et al 2010), an area involved in perception of pain and empathy, as well as processing of disgust. However these deficits in emotion processing in BPD have not previously been investigated with regards to a measure of childhood experience.

Although facial emotion recognition has been previously examined in some studies of BPD, tests of social cognition have not been so extensively explored. The term 'social cognition' refers to the way in which we gather information that allows us to make judgements about characteristics of other people, including personality and intentions. Key to social cognition is the process of mentalisation, which enables us to attribute mental states to the people around

us – how they may feel or think in a given situation (Fonagy et al 2011, Choi-Kain and Gunderson 2008). Effective social functioning requires the involvement of a network of brain areas in order to gather, retrieve and process relevant information in the correct way, and is fundamental not just in cultivating relationships with others, but for everyday functioning and social interaction of all kinds. A very important source of social information is the face, and consequently, one major means through which social brain function has been investigated in healthy volunteers and patient groups has been through the study of face perception (Young and Bruce 2011). Investigations of social perception from faces have implicated several brain areas as important in social cognition, including the medial frontal cortex, the amygdala, the insula, the cingulate cortex and precuneus, regions of superior temporal cortex and the fusiform gyrus (Mar 2011, Adolphs 2010, Marwick and Hall 2008, Amodio and Frith 2006, Winston et al 2003, Adolphs et al 1998).

Previous studies have investigated social cognition in BPD using a range of measures. Hill and colleagues, demonstrated impairments in social function in BPD using the RAPFA (Revised Adult Personality Functioning Assessment), an interview-based technique (Hill et al 2010). Preissler et al (2010) asked BPD patients to complete two tests of social cognition – one, the RME (Reading the Mind in the Eyes) task, involved participants inferring the mental state of individuals by viewing pictures of the eye region only, and the other, the MASC (Movie for the Assessment of Social Cognition), required participants to attribute mental states to characters in a short film. Although the RME task did

not reveal a significant difference in performance between the BPD and healthy control groups, scores in the MASC were significantly lower in the patient group compared to the control group, providing evidence of deficits in social functioning and mentalisation in BPD. These findings are consistent with previous structural imaging studies of BPD, which have found that brain areas involved in social cognition, including frontal and medial temporal lobe regions, are altered in volume in the disorder (Hall et al 2010b, Mauchnik and Schmahl 2010, Brunner et al 2009, Nunes et al 2009, Soloff et al 2008, Tebartz van Elst et al 2003). However, despite the overlap between structural abnormalities in BPD and the brain areas known to be involved in social decision making from faces, there have been no previous studies of deficits in social judgement from faces in BPD.

Here, we address these issues by testing a group of participants with a diagnosis of BPD and a group of healthy control participants on a test of emotion recognition, as well as a test of social judgement from faces. Both groups completed the Ekman 60 Faces Test (Young et al 2002, Ekman and Friesen 1976) to give a measure of emotion recognition from faces and, in keeping with the studies described above, we hypothesised that those with a diagnosis of BPD would be less well able to correctly identify facial emotions than control participants.

Since faces convey a great deal of social information, and face processing has been studied extensively in health and in other disorders, we anticipated that

studying the performance of individuals with BPD on tests of social judgement from faces would allow a more detailed characterisation of the areas of deficit in social function in BPD. Although we appreciate that the test does not entirely represent a "real-world" situation, we believe that it can provide important information about the cognitive underpinnings of the disorder. In order to arrive at a more precise characterisation of areas of relative strength and weakness in social decision making in individuals with BPD, we chose characteristics that included those with a clear and relatively well-established physical basis (age, distinctiveness, attractiveness) and those with a more purely social function involving an inference about a psychological trait or disposition (intelligence, approachability, trustworthiness).

We hypothesised that differences between groups would be evident in those judgements that required inferences about mental state and, in particular, that the BPD group would perform significantly poorer that controls in judgements related to the perception of threat (approachability and trustworthiness).

All participants completed the Childhood Trauma Questionnaire (CTQ) – a self report measure of childhood adversity, and this data was used to investigate the relationship between childhood adversity and performance on both the Ekman 60 Faces Test and the test of social judgement from faces. We hypothesised that a relationship would be evident between severity of childhood trauma and performance on both tests, such that greater severity of trauma would correlate with lower test scores.

3.2. Methods

Participants and Questionnaires

Detailed participant information, including demographics and inclusion/exclusion criteria can be found in chapter 2. Briefly, 20 participants meeting DSM-IV criteria for borderline personality disorder were recruited for the study from outpatient populations, and 21 matched control participants were recruited from the community. All participants completed the Hamilton Rating Scale for Depression (HAM-D), Young Mania Rating Scale (YMRS) and Childhood Trauma Questionnaire (CTQ). All participants also completed the National Adult Reading Test (NART) as a measure of IQ. The study was approved by the Local Research Ethics Committee and informed consent was obtained from all participants.

Emotion recognition

As detailed in chapter 2, participants completed the Ekman 60 Faces Test, in which they viewed a series of 60 photographs of faces, displaying one of the six universally recognised facial emotions – anger, disgust, fear, happiness, sadness or surprise. The names of all six emotions were listed on the screen below each photograph, and participants made a selection by clicking the mouse over the desired name. The next face was not shown until a selection had been made.

Participants were shown six practice images, covering the six emotions, which were not included in the analysis.

Social judgement

As detailed in chapter 2, participants completed a test of social judgement from faces involving six blocks of trials in which participants judged whether each of a set of 32 photographs of faces was 'high' or 'low' on a specified characteristic (Santos and Young 2008, Hall et al 2004). The characteristics to be judged in each block of trials were age, distinctiveness, attractiveness, intelligence, approachability and trustworthiness.

Only a single characteristic was judged in each block of 32 trials. Faces appeared on a computer screen for 3 seconds each and participants were asked to choose from two options for the judged characteristic (eg “trustworthy” or “untrustworthy”). Judgements were reported verbally to the experimenter, and there was no limit on how long participants were given to make a choice, but the next picture was not shown until a judgement had been made. Answers were recorded by the experimenter but no feedback was provided. Participants were given an 8 practice images before each block of trials; these were not included in the analysis.

Statistical Analysis

Statistical analysis was carried out using IBM SPSS, version 19.0 for Windows. T-tests were used to investigate mean differences between the BPD and control groups in age, IQ, YMRS, HAM-D and CTQ scores.

Repeated measures Analyses of Variance (ANOVA) was used to investigate performance in the social judgment tasks with judged characteristic as the within subject variable and group as the between subject factor. Following the investigation of effects of group, effects of characteristic and group x characteristic interactions, the effect of group was investigated for each emotion separately using independent t-tests. In order to correct for multiple comparisons only effects that survived False Discovery Rate correction (Benjamini and Hochberg 1995) at $p < 0.05$ were considered significant.

Repeated measures ANOVA was also used to analyse subjects' performance in the Ekman 60 Faces test, with group (BPD/control) as the between subjects factor and stimulus (emotion) as within subjects variable. Where recognition of individual emotions (eg happiness) was compared, T-tests were used.

3.3. Results

Demographic Characteristics

There was no difference in age ($t_{1,39}$ = -0.07, p = 0.94) or IQ ($t_{1,37}$ = 0.73, p = 0.47) between the control and BPD groups (table 3.1). However two individuals from the BPD group and one from the control group chose not to complete the NART, and so were excluded from IQ analysis. The BPD group scored significantly higher than controls on the HAM-D ($t_{1,39}$ = 7.77, p < 0.001), the YMRS ($t_{1,39}$ = 4.83, p < 0.001) and the CTQ ($t_{1,39}$ = 9.39, p < 0.001) (table 3.1)

	BPD			Healthy control		
Demographics	n	mean	SD	n	mean	SD
Age	20	34.3	8.5	21	34.5	11.6
IQ	20	115.9	7.4	21	114.2	7.3
CTQ	20	37.4	17.6	21	1.2	1.7
HAM-D	20	14.5	8.3	21	0	0
YMRS	20	2.5	2.4	21	0	0
Number of BPD criteria (max 9)	20	7.4	1.3	21	0	0
Medication	n	%				
Antipsychotic medication	11	55				
Antidepressant medication	13	65				
Comorbid diagnoses	n	%				
Total	14	70				
Bipolar affective disorder ii	4	20				
Eating disorder	6	30				
PTSD	2	10				
OCD	2	10				
Other	3	15				

Table 3.1. Participant demographic information

Emotion recognition

Repeated measures ANOVA was used to analyse subjects' performance in the Ekman 60 Faces test, with group (BPD/control) as the between subjects factor and stimulus (emotion) as within subjects variable. The results showed significant effects of emotion ($F_{5,195} = 17.4$, $p < 0.001$) and group ($F_{1,39} = 6.2$, $p =$

0.02), and an emotion x group interaction ($F_{5,195}$ = 2.7, p = 0.02). Further analysis by *post-hoc* T-tests revealed that the overall group effect was contributed to substantially by impaired recognition of disgust in the BPD group ($t_{1,39}$ = -3.5, p = 0.001), with no other emotion reaching significance (figure 3.1). The deficit in disgust recognition remained significant following application of the FDR correction, and even the Bonferroni correction for multiple comparisons (p Bonferroni corrected <0.01).

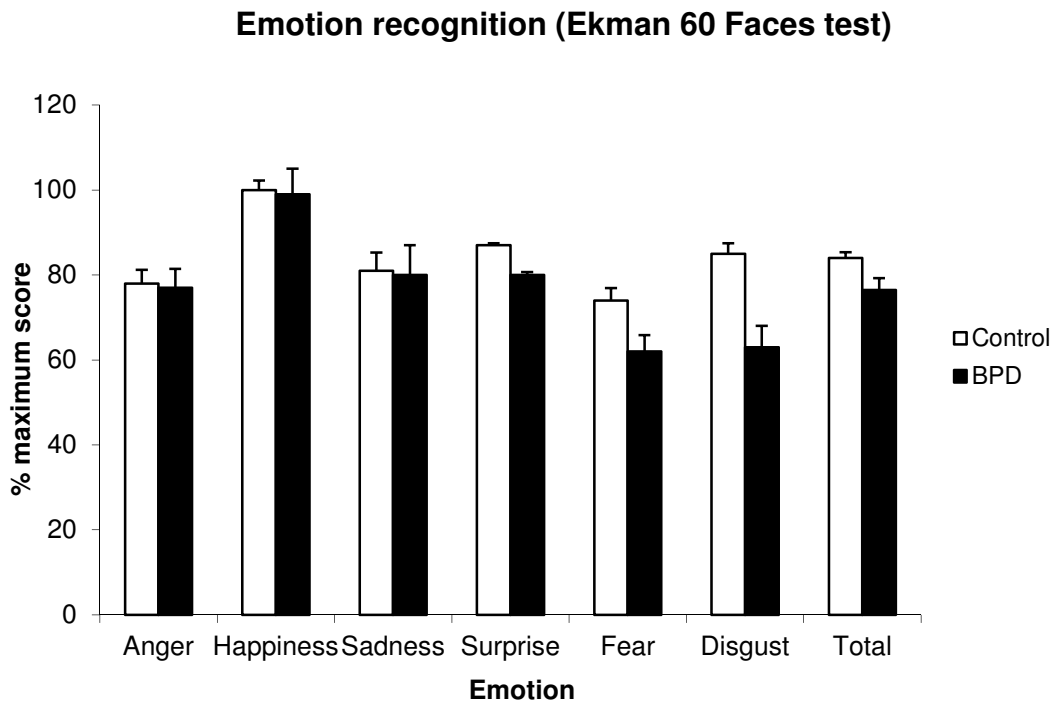


Figure 3.1. Emotion recognition scores. Graph showing recognition of each of the six emotions. The BPD group showed particular deficits in the recognition of disgust.

Emotion recognition correlation analysis

We next investigated the relationship between childhood trauma, as measured by the CTQ, and emotion recognition in BPD. Total CTQ scores were found to correlate with Ekman 60 Faces test performance in the BPD group, with poorer performance associated with a higher CTQ score ($r = -0.48$, $p = 0.03$). Following separation of the CTQ questions into five subgroups, significant correlations were apparent between emotion recognition (Ekman 60 Faces test score) and physical abuse ($r = -0.49$, $p = 0.03$), as well as emotional abuse ($r = -0.48$, $p = 0.03$), but not between emotion recognition and sexual abuse ($r = -0.33$, $p = 0.15$), physical neglect ($r = -0.11$, $p = 0.67$) or emotional neglect ($r = -0.21$, $p = 0.37$).

Correlation analysis between CTQ scores and individual emotions revealed that disgust recognition was the main contributor to the overall significant relationships between emotion recognition and total CTQ score ($r = -0.47$, $p = 0.04$), the physical abuse subscale ($r = -0.49$, $p = 0.03$), and the emotional abuse subscale ($r = -0.48$, $p = 0.03$). There was no significant correlation between any of the other specific emotions and CTQ scores and no significant correlation was found between performance on the Ekman 60 Faces test and either the Hamilton Rating Scale for Depression ($r = -0.21$, $p = 0.38$, or the Young Mania Rating Scale ($r = 0.05$, $p = 0.83$).

Social judgement

Performance in the test of social cognition was analysed using repeated measures ANOVA, using group as the between subjects factor and judged characteristic (age, distinctiveness, attractiveness, intelligence, approachability, trustworthiness) as a within subjects factor. There was a significant main effect for group ($F_{1,39} = 12.2$, $p = 0.01$) and judged characteristic ($F_{5,195} = 23.3$, $p < 0.01$) but no significant interaction between the two ($F_{5,195} = 1.9$, $p = 0.1$). Overall the BPD group showed a difference in social task performance compared to controls. *Post-hoc* t-tests revealed that the between-group differences were greatest for the tests of approachability ($t_{1,39} = -3.1$, $p = 0.004$), trustworthiness ($t_{1,39} = -2.5$, $p = 0.014$) and intelligence ($t_{1,39} = -2.1$, $p = 0.043$), but were not significant for the other social dimensions (age ($t_{1,39} = -1.8$, $p = 0.087$); attractiveness ($t_{1,39} = -0.81$, $p = 0.420$); distinctiveness ($t_{1,39} = -1.67$, $p = 0.101$)). Only the results for the approachability and trustworthiness tests remained significant at $p < 0.05$ after FDR correction for the multiple comparisons made (figure 3.2.).

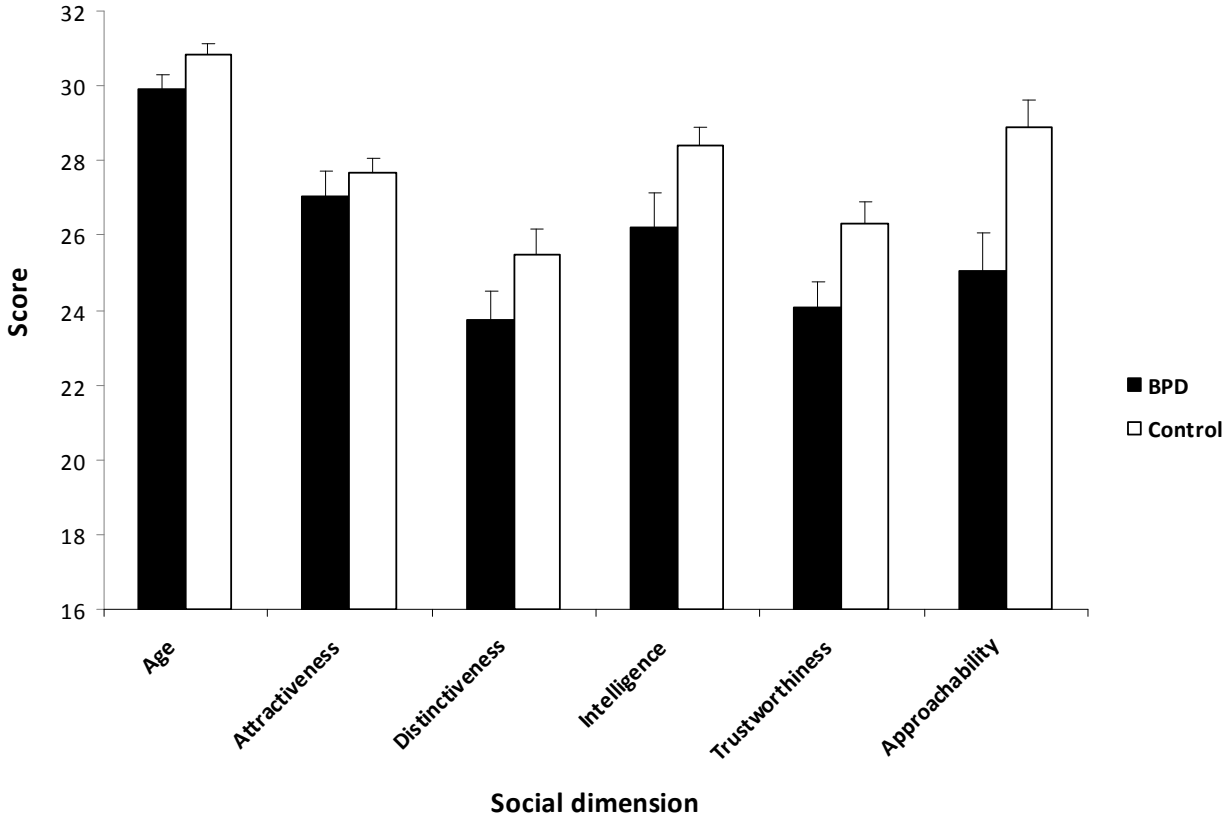


Figure 3.2. Social judgement scores. Graph of social judgement scores for each of six dimensions. The BPD group scored significantly lower than the control group on judgements of trustworthiness and approachability.

Judgement bias analysis

In order to assess whether there was any bias in the direction of social judgements of approachability and trustworthiness made by the BPD group, deviations from the expected answer given by participants when judging approachability and trustworthiness were counted and the direction of change recorded (for example, judging approachable as unapproachable or judging unapproachable as approachable). Repeated measures analysis of variance

revealed a group x error direction interaction for judgements of approachability ($F_{1,39}$ = 6.3, p = 0.016) and trustworthiness ($F_{1,39}$ = 14.1, p = 0.001). *Post hoc* t-tests revealed that these effects derived from the BPD group judging more faces as unapproachable ($t_{1,39}$ = 3.5, p = 0.001) and untrustworthy ($t_{1,39}$ = 4.2, p = 0.007) than the control group (figure 3.3.).

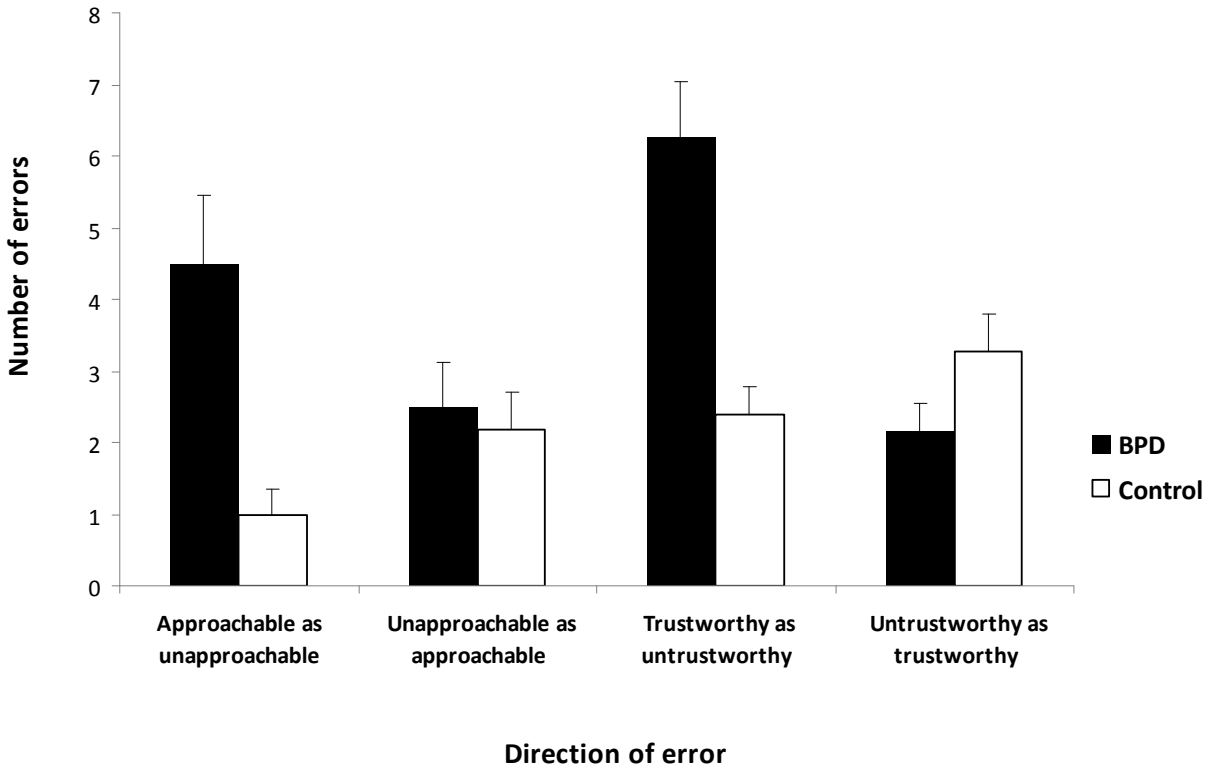


Figure 3.3. Social judgement bias. Graph showing the direction of judgement bias for approachability and trustworthiness. The BPD group judged significantly more people as unapproachable and untrustworthy than the control group.

Social judgement correlation analysis

Correlation analysis revealed no significant correlation between the HAM-D, CTQ, or YMRS and the number of errors on each social judgement task made by participants in either the control or BPD group. However, a significant correlation was noted in the BPD group between Childhood Trauma Questionnaire scores and bias towards judging faces as unapproachable ($r = 0.49$, $p = 0.029$). Examination of the subscales of the CTQ revealed that this correlation was strongest for the sexual abuse subscale of the CTQ ($r = 0.53$, $p = 0.016$). No other correlation was found between social judgement bias and clinical measures.

3.4. Discussion

Participants with a diagnosis of BPD performed less well than controls in a test of social judgement from faces and a test of emotion recognition. Those in the BPD group scored lower overall than healthy participants and, in particular, this group had difficulty judging trustworthiness and approachability, and recognition of disgust was particularly impaired. Notably, the BPD group judged more faces as unapproachable and untrustworthy than the control group, and bias towards judging approachable faces as unapproachable in those with BPD correlated with childhood trauma scores as measured by the CTQ. The ability of those with a diagnosis of BPD to recognise the facial emotion of disgust also

correlated significantly with CTQ scores. Following separation of the CTQ questions into their five subgroups - physical abuse, emotional abuse, sexual abuse, physical neglect and emotional neglect – we found that only scores relating to physical abuse and emotional abuse correlated significantly with emotion recognition in the BPD group.

Emotion recognition

The present results suggest that childhood experience has a lasting effect on the emotional brain, and that negative experiences may contribute to the symptoms experienced by those with BPD in adulthood. In particular, difficulties in correctly recognising facial emotions is likely to play a part in the social difficulties suffered by individuals with BPD, given that such a large amount of the information we glean about others comes from the face (Young and Bruce 2011).

Neural processing of disgust involves the insular cortex (Ibanez et al 2010), an area of the brain which is also associated with empathy and perception of pain, and which has been shown to have altered function in studies of BPD (Niedtfeld et al 2010). Recent evidence also suggests that changes in the structure of the insular cortex may be related to early-life trauma (Ansell et al 2012), and Olesen and colleagues (2010) have shown that prolonged experience of pain leads to functional reorganisation of this area. The current finding, of a highly significant

correlation between CTQ score and disgust recognition in the BPD group, indicates that childhood trauma may play a part in altered insular cortex structure or functional reorganisation, leading to difficulties in emotion processing in this area.

The present findings demonstrate that people with BPD have difficulty correctly perceiving emotions in faces, particularly the emotion of disgust, and that this difficulty is associated with traumatic childhood experiences.

Social judgement

Todorov and his colleagues (Oosterhof and Todorov 2008, Todorov et al 2008b), have developed an important perspective on how social characteristics are evaluated in faces that suggests they are based on orthogonal dimensions involving the appraisal of valence (positive or negative intentions) and dominance (ability to enact intentions). In this approach, the appraisal of trustworthiness and approachability are closely linked to the valence factor, raising the interesting possibility for future research that it may be this factor that is particularly affected in BPD.

More generally, both approachability and trustworthiness judgements are related to threat detection, as incorrectly judging a person as approachable or trustworthy could have potentially hazardous consequences. Although efficient

social functioning requires a network of brain areas for information processing, it is the amygdala that is principally involved in fear and threat detection, and this area has been shown consistently to be necessary for normal social cognition in animal and human studies (Adolphs 2001). There is evidence from neuropsychology (Adolphs et al 1998) that the amygdala plays a role in social judgements and functional brain imaging studies have also reported amygdala involvement in the judgement of trustworthiness (Todorov et al 2008, Winston et al 2002) and approachability (Hall et al 2010a). Martens and colleagues (2009) also noted a relationship between amygdala volume and approachability in patients with Williams syndrome, with increased amygdala volume correlating with higher approachability ratings of faces. Patients with BPD have been shown to have decreased amygdala volume in structural MRI studies, and heightened amygdala responses to facial stimuli in functional MRI studies (Hall et al 2010b, Nunes et al 2009, Minzenberg et al 2007, Donegan et al 2003). The present findings are therefore consistent with suggestions of heightened amygdala-mediated threat responses to facial and social stimuli in BPD.

Our findings also indicate that skewed perception of approachability in those with a diagnosis of BPD is specifically related to childhood adversity, suggesting that trauma in childhood has a sustained and lasting impact on social cognition in BPD. Although the neurobiological substrates of this effect are not known, childhood adversity has recently been related to enhanced amygdala reactivity in a healthy population sample (Dannlowski et al 2012) and in major depressive

disorder (Grant et al 2011), suggesting that childhood trauma may alter social judgement in BPD by modulating amygdala activation (Donegan et al 2003).

The current results are also consistent with a broader dysfunction in brain networks sub-serving social cognition and mentalising in BPD. Previous studies in healthy individuals have demonstrated the importance of a number of brain regions in social decision-making including the medial prefrontal cortex, inferior prefrontal cortex, cingulate cortex and superior temporal cortex (Mar 2011, Hall et al 2010a, Winston et al 2002, Adolphs 2001). Structural imaging studies of patients with BPD have also shown altered structure of distributed brain regions implicated in social cognition including reductions in columes of regions of the frontal and medial temporal lobes (Hall et al 2010b, Nunes et al 2009, Brunner et al 2009, Soloff et al 2008, Tebartz van Elst et al 2003). Furthermore, dysfunctional connectivity between the amygdala and PFC has been reported in studies of BPD (Wolf et al 2011, New et al 2007). Taken together with these previous findings, our present results suggest deficits in approachability and trustworthiness judgements may derive from a wider disruption of fronto-limbic circuits in BPD, with a failure of frontal regions to regulate affective responses in individuals with the disorder.

The current findings suggest that individuals with BPD have difficulties in mentalising, which are distinct from those seen in other neuropsychiatric disorders. The pattern of deficits we observed in the tests of social judgement in individuals with BPD differed from those seen on the same tests in patients with

schizophrenia (Hall et al 2004), patients with autism (Philip et al 2010), and patients with depression (Hall et al unpublished data). These results suggest a degree of specificity to the impairment in mentalising ability in individuals with BPD, which may be particularly related to increased sensitivity to threat.

Taken together, the results from this study indicate that those with a diagnosis of BPD show significant impairment in gathering and processing information from faces. The heightened responsiveness of sufferers to potentially threatening situations, illustrated by increased judgements of trustworthy faces as untrustworthy and approachable faces as unapproachable, has clinical implications for the management of patients. Patients with BPD are more likely to view neutral situations as threatening, and may require more reassurance and assistance in understanding social cues than other psychiatric patients. Similarly, the diminished ability of this group to accurately identify facial expressions of emotion may further inhibit their ability to correctly understand the intentions of others. It has been suggested that deficits in mentalisation may underpin many of the core features of BPD, including social difficulties (Fonagy et al 2011), and our results are consistent with this idea, supporting the potential value of mentalisation based therapies as a treatment for individuals with a diagnosis of BPD (Bateman and Fonagy 2010).

4. Brain structure in BPD – grey matter volume

4.1. Introduction

A growing body of work has been undertaken in recent years in order to identify the neurobiological underpinnings of the disorder and its symptomatology and, as a result, structural neuroimaging studies have shed light on brain areas that may be abnormal in those with a diagnosis of BPD.

Traditional structural imaging techniques involved assessing volume by the manual tracing of structures. However, automated statistical techniques, such as VBM, are now widely used, and have comparable results to manual tracing (Whitwell 2009). The most prevalent findings in structural neuroimaging studies of BPD are of reduced grey matter volume in the hippocampus and amygdala compared to healthy controls (Niedtfeld et al 2013, Soloff et al 2008, Schmahl et al 2003, Tebartz van Elst et al 2003, Driessen et al 2000, or for recent reviews see Krautz-Utz et al 2014, O'Neill and Frodl 2012). However, while reduced hippocampal volume bilaterally is a consistent finding, results concerning amygdala volume in BPD are disputed. Rather than volume reduction, some studies have reported no differences in amygdala volume between groups (Schmahl et al 2009, New et al 2007, Zetzsche et al 2006, Brambilla et al 2004), and others have reported an increase in amygdala grey

matter volume in those with BPD compared to controls (Minzenberg et al 2008).

It has been suggested that the inconsistent amygdala findings may be due to the different subtypes of BPD (Mauchnik and Schmahl 2010). With five of nine criteria required for a diagnosis, as well as individual variation in symptom severity, it is possible that many individuals with the same diagnosis could have very different symptoms and experience of the disorder (see chapter 1). Another reason for such discrepancies may be the relatively small study sample sizes (Nunes et al 2006). Ruocco et al (2012), Hall et al (2010) and Nunes et al (2009) attempted to overcome the issue of small sample size by conducting meta-analyses of several neuroimaging studies, with all groups reporting smaller amygdala volumes in those with a diagnosis of BPD compared to healthy controls.

Aetiological factors may also contribute to structural brain changes in BPD, and several studies have found correlations between grey matter volume and childhood trauma. Increased grey matter volume in the hypothalamus has been reported in BPD compared to controls (Kuhlmann et al 2013). This change is likely due to abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, which is responsible for the neuroendocrine response to stress. The same study also found that hypothalamic volume in the BPD group correlated positively with history of trauma, as measured by the CTQ, a finding that was not replicated with hippocampal, amygdala or ACC volumes. However, Brambilla et

al (2004) did report reduced hippocampal volume in those with BPD compared to healthy controls, which correlated with childhood abuse. In addition, Driessen et al (2000) found a correlation between extent and duration of trauma, using a modified version of the CTQ, and grey matter volume in the hippocampus and amygdala, but only when those with BPD and healthy controls were considered together. Similarly, Dannlowski et al (2012) found a significant association between childhood trauma and right hippocampal volumes in healthy participants, as well as reduced volumes in the insula, OFC, ACC and caudate in those with high CTQ scores. This finding suggests that volume reductions in these areas may be a result of childhood maltreatment, and not BPD per se. However, few studies have attempted to correlate grey matter volume abnormalities with measures of childhood trauma, so any conclusions should be treated with caution. In addition, a study of first presentation BPD in teenagers found no correlation between childhood maltreatment and grey matter volume (Chanen et al 2008, Whittle et al 2008).

Studies in adolescents with first-presentation BPD have revealed that structural brain abnormalities are present at this early stage in the disorder, with reduced grey matter volume in the ACC (Whittle et al 2009), DLPFC (Brunner et al 2010) and OFC (Brunner et al 2010, Chanen et al 2008). No differences in grey matter volume were reported between those with BPD and healthy control participants. Taken together with studies of adults with a diagnosis BPD, it appears that structural brain changes develop with time in the disorder. Indeed,

Hall et al (2010) reported a significant effect of age on hippocampal volume in BPD.

Here, we aimed to investigate grey matter volume in a group of participants with a diagnosis of BPD compared to healthy controls. Based on previous structural imaging studies, we expected to find differences between groups in the hippocampus and amygdala, perhaps extending into the OFC and DLPFC. We also aimed to relate any group differences to experience of childhood trauma, as measured by the CTQ, expecting to find a link between severity of abuse and abnormalities in grey matter volume in BPD.

4.2. Methods

Participants and questionnaires

Participant information, including demographics and inclusion/exclusion criteria are detailed in chapter 2. Briefly, 20 individuals with a diagnosis of BPD were recruited from outpatient populations, and 16 matched healthy control participants were recruited from the community. All participants completed the same clinical exam and questionnaires as follows: current psychotic symptoms were rated using the positive symptom component of the Positive and Negative Syndrome Scale (PANSS) (Kay et al 1987), current symptoms of depression were

rated using the Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960), and current symptoms of mania were rated using the Young Mania Rating Scale (YMRS) (Young et al 1978). Severity of BPD symptoms (where present) was assessed using the Zanarini rating scale for BPD (Zanarini 2003). Participants additionally completed the CTQ (Bernstein et al 1997), a self-report measure of childhood maltreatment.

SMRI acquisition

Imaging data was acquired using a 3T Siemens Magnetom Verio Syngo MR scanner, collected at the Clinical Research Imaging Centre (CRIC), University of Edinburgh.

The MP-RAGE for use in analysis was acquired using the following parameters: repetition time (TR) 2300 ms, echo time (TE) 2.98 ms, flip angle 9°, slice thickness 1 mm.

SMRI analysis

Data processing was carried out using Statistical Parametric Mapping Software (SPM8, Wellcome Trust Centre for Neuroimaging) and run using MATLAB software version 7.13 (MathWorks).

Further details of the sMRI analysis can be found in chapter 2. Briefly, study specific templates were created from participant data using the DARTEL method to improve registration.

The general linear model (GLM) was then used to compare grey matter volume between the control and BPD participant groups using t and F tests. Whole brain VBM was conducted, with the threshold set at 0.005. A small volume correction was also applied for the hippocampus/amygdala using the WFU pickatlas software, based on our hypothesis that grey matter volume in these areas was likely to be different between groups.

4.3. Results

Demographic, clinical and behavioural data

There was no difference in age ($t_{1,36}$ = -3.82, p = 0.97) or IQ ($t_{1,31}$ = -0.56, p = 0.58) between groups. Five control participants did not complete the National Adult Reading Test and these individuals were excluded from IQ analysis. The

BPD group scored significantly higher on the HAM-D ($t_{1.36}$= -8.07, $p < 0.001$), YMRS ($t_{1,36}$ = -2.92, $p < 0.01$), PANSS ($t_{1,36}$ = -4.34, $p < 0.001$) and childhood trauma questionnaire ($t_{1,35}$ = -6.99, $p < 0.001$) than the control group. All participants showed good engagement with the fMRI task (99.4% response rate). Participant information is detailed in table 4.1.

	BPD			Healthy control		
Demographics	n	mean	SD	n	mean	SD
Age	20	35.8	8.6	16	34.8	9.6
IQ	20	114.8	7.9	16	114.5	6
CTQ	20	52.9	19.8	16	13.1	11.5
HAM-D	20	15.5	8.6	16	0	0
YMRS	20	2.1	3.1	16	0	0
PANSS above baseline	20	2.6	2.5	16	0	0
ZAN-BPD	20	13.7	6.7	16	0	0
Medication	n	%				
Antipsychotic medication	12	60				
Antidepressant medication	15	75				
Comorbid diagnoses	n	%				
Total	17	85				
Depression	4	20				
Bipolar affective disorder ii	4	20				
Eating disorder	3	15				
PTSD	2	10				
OCD	2	10				
Other	2	10				

Table 4.1. Participant information

VBM

We found no significant differences in grey matter volume between groups for either contrast BPD > control or control > BPD. There was also no correlation found between grey matter volume and PANSS, HAM-D, YMRS or CTQ scores in the BPD group.

4.4. Discussion

Our present findings, of no difference in grey matter volume between those with a diagnosis of BPD and healthy controls in any brain region, including the hippocampus and amygdala, was in contrast to our hypothesis. While this result is not consistent with much of the previous literature, some other studies have reported no differences in grey matter volume between BPD and control groups in the hippocampus (Schmahl et al 2009, Tebartz van Elst et al 2007) and amygdala (Schmahl et al 2009, New et al 2007, Zetzsche et al 2006, Brambilla et al 2004).

The reasons for such inconsistencies in the literature regarding structural abnormalities in BPD are unclear. It may be that grey matter volume changes in

BPD are subtle, or may change with increasing time course of the disorder. It is also important to note VBM only gives a measure of grey matter volume, and not of other structural measures, so using this method alone may not give a full picture of any structural brain changes in BPD. Measurements of cortical thickness are now possible using other software, such as Freesurfer (Fischl 2012). Using this method, the shape and texture of brain structures can also be examined, which is not possible using VBM. It may be the case that structural changes other than those of grey matter volume are present in BPD. In fact, in an extension of the current work, diffusion tensor imaging (DTI) analysis carried out on the same sample revealed decreased white matter tract integrity in the cingulum and fornix in BPD (Whalley and Nickson et al, submitted). This finding illustrates not only structural, but also connectivity abnormalities in those with a diagnosis of BPD. It therefore appears prudent to investigate as many aspects of brain changes as possible in a given data set, in order to assemble a more complete picture of the biological underpinnings of the disorder. However VBM remains an effective method for quickly and efficiently assessing grey matter volume differences between groups, and is especially useful when large sample sizes are involved.

As mentioned previously, there has been suggestion that group size and BPD subgroup type could contribute to the literature inconsistencies. The current study recruited a similar number of participants as previous studies, which had between 12 and 25 participants per group, and also reported no differences in

grey matter volume between groups (Schmahl et al 2009, Tebartz van Elst et al 2007, Zetzsche et al 2006). However, some studies with even smaller group sizes than in the current study did report some grey matter volume differences between BPD and controls (Sala et al 2011, Brambilla et al 2004, Schmahl et al 2003, Tebartz van Elst et al 2003), casting doubt on this theory. It is also true that other structural analyses, namely DTI, did find group differences in the current participant sample. It may be, then, that grey matter volume differences are more subtle in BPD than other structural changes, and are more difficult to detect.

The idea that BPD subtype may contribute to the discrepancies in results between studies is likely to be valid and, indeed, may be relevant for all research into the disorder. The DSM-IV states nine criteria for BPD, of which a minimum of five must be met for a diagnosis. Therefore, some individuals with a diagnosis of BPD may meet all nine criteria, some may meet eight, some seven etc, and if all criteria are not met, those which are will vary between patients. In total there are 256 combinations possible for a diagnosis of BPD to be given (Ellis and Abrams, 2009). There are, then, a myriad of symptoms and behaviours that may be experienced and elicited by individuals who have such a diagnosis, and only some of these may relate to specific structural brain abnormalities. While this issue cannot be overcome, it would be helpful if future studies included data describing which criteria are met for each participant, and the symptom severity. Even better would be to separate participants into specific subgroups

in order to gain some real insight into the reasons behind any grey matter volume differences between those with BPD and healthy controls. However this, again, presents potential problems of sample size.

Overall, while the present study did not identify any differences in grey matter volume between those with a diagnosis of BPD and healthy control participants, it has highlighted some important methodological and reporting shortfalls. Understanding of the neurobiological underpinnings of BPD remains poor; however, research in this area has been increasing, and future studies could help increase their contributions to the field by ensuring careful participant selection, thorough symptom classification and data transparency.

5. Functional activation in response to emotional faces in BPD

5.1. Introduction

Several studies have shown that individuals with BPD have altered responses to emotional stimuli, such as emotional facial expressions (Daros et al 2013, Levine et al 1997, for review see Mitchell et al 2014). There is also increasing evidence that neutral or positive facial expressions are more commonly perceived as negative by those with BPD (Domes et al 2009, Dyck et al 2009, Meyer et al 2004, Wagner and Linehan 1999). Furthermore, our work has revealed a correlation between facial emotion recognition in the disorder and experience of childhood physical abuse (see chapter 3) suggesting a potential link between childhood adversity and later responses to emotional stimuli in BPD.

Tests of facial emotion recognition during fMRI have revealed activation differences between those with BPD and healthy controls, with increased amygdala activation most commonly reported in the disorder (Mier et al 2013, Guitart-Masip et al 2009, Minzenberg et al 2007, Donegan et al 2003). Dysfunctional activation in the amygdala in response to facial expressions may

help to explain the emotional difficulties experienced by those with a diagnosis of BPD, given the role of this area in general emotion processing (Aggleton and Mishkin 1986). All of these studies tested recognition of a range of emotions, so activation changes in response to any single emotion cannot be easily identified from the existing literature.

Emotional stress is known to increase the prevalence and experience of psychotic symptoms in BPD (Schroeder et al 2013, Glaser et al 2010), illustrating the sensitivity of sufferers to emotionally arousing stimuli. Research has indicated that childhood adversity may contribute to risk of developing psychotic symptoms more generally (Varese et al 2012, Read et al 2005), therefore childhood trauma may contribute to vulnerability for the development of psychotic symptoms in BPD. The mechanism associating childhood adversity and the development of psychotic symptoms in disorders such as BPD is, however, unclear. One possibility is that early life experience modifies the function of the midbrain dopaminergic system. Dopamine signalling dysfunction has been established as playing an important role in the symptoms of psychosis experienced in schizophrenia (Howes and Murray 2013), and its receptors are the common target of antipsychotic therapeutics, which have been shown to have some efficacy in BPD (Gross and Drescher 2012, Ingenhoven and Duivenvoorden 2011, Lieb et al 2010). A potential role of the midbrain in the development of psychotic symptoms is further supported by Felmingham et al (2010), who found that women with a history of childhood abuse displayed abnormal midbrain activation in response to fearful faces.

Here, we sought to investigate brain activation in response to particular emotional faces in BPD, utilising well validated stimuli from the pictures of facial affect (Ekman and Friesen 1976). Based on our neuropsychology work we hypothesised that brain activation in response to emotional faces in BPD would be modified by prior experience of childhood adversity. We expected that activation would relate to current symptom severity, in particular severity of psychotic symptoms, based on literature linking emotional dysfunction and psychotic symptoms. In particular, we expected to find between group differences and/or correlations with symptoms in insula activation in response to disgusted faces, and between group differences and/or correlations with symptoms in amygdala in response to fearful faces. In addition, we aimed to investigate midbrain activation in response to fearful faces, and its relationship to childhood abuse and psychotic symptoms.

5.2. Methods

Participants

Detailed participant information including inclusion/exclusion criteria can be found in chapter 2. Briefly, 20 individuals with a diagnosis of BPD were recruited from outpatient populations, and 16 matched controls were recruited

from community volunteers. . Current psychotic symptoms were rated using the positive symptom component of the Positive and Negative Syndrome Scale (PANSS) (Kay et al 1987), current symptoms of depression were rated using the Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960), and current symptoms of mania were rated using the Young Mania Rating Scale (YMRS) (Young et al 1978). Severity of disorder symptoms was assessed using the Zanarini rating scale for BPD (Zanarini 2003).

FMRI task

A detailed description of the fMRI task can be found in chapter 2. In the scanner, participants performed a task that involved viewing a photograph of a face on a computer screen, and selecting whether they thought the face was male or female, indicated by pressing the corresponding response button. Faces were chosen from the Ekman series of emotional faces (Ekman and Friesen 1976) and displayed either a fearful, disgusted or neutral expression.

fMRI data acquisition and analysis

Imaging data was acquired using a 3T Siemens Magnetom Verio Syngo MR

scanner. Functional imaging scans were acquired using the following parameters: repetition time (TR) 1560 ms, echo time (TE) 26 ms, flip angle 66°, 26 slices (slice thickness 5 mm), field of view (FOV) 220 x 220 mm, voxel size 3.5 x 3.5 x 5 mm.

Additional data processing details can be found in chapter 2. Data processing was carried out using Statistical Parametric Mapping Software (SPM8, Wellcome Trust Centre for Neuroimaging) and run using MATLAB software version 7.13 (MathWorks). The first 6 images were discarded, and the remaining images realigned to the mean image. The realigned images were then co-registered to the corresponding T1 weighted anatomical images, and these were spatially normalised into the Montreal Neurological Institute (MNI) brain template. Finally, the normalised data was smoothed with a 3-dimensional isotropic Gaussian kernel (8 mm full width at half maximum).

Statistical analysis was performed in SPM8 separately for each task (fear and neutral, and disgust and neutral). Data was modelled for conditions “emotion” (fear or disgust) and “neutral” for each participant, and contrast images generated. The primary comparison of interest was the contrast of emotional versus neutral faces for each task. Second-level analysis was carried out to compare differences within and between groups using t-tests. The whole-brain threshold was 0.005 for all analyses, and p values are reported FWE corrected, unless otherwise stated. Within group regression analysis was performed across

all participants in the BPD group using scores on the PANSS, HAM-D, YMRS and childhood trauma questionnaire, in order to identify areas of brain activation that correlated with clinical data. In line with our prior hypotheses that childhood trauma would have a particular impact on brain regions involved in emotional and motivation processing we applied a small volume correction for activation within the amygdala. A midbrain / ventral striatum small volume correction was also applied to the fear task data, as used previously (Romaniuk et al 2010), supported by previous results indicating a relationship between childhood trauma and brainstem responses to fearful faces in women (Felmingham et al 2010).

Further statistical analysis was carried out using SPSS software version 19. Demographic and clinical characteristics between groups were compared, and activation data was extracted from SPM for use in SPSS correlation analysis in the BPD group.

5.3. Results

Demographic, clinical and behavioural data

There was no difference in age ($t_{1,36}$ = -3.82, p = 0.97) or IQ ($t_{1,31}$ = -0.56, p = 0.58) between groups. Five control participants did not complete the National

Adult Reading Test and these individuals were excluded from IQ analysis. The BPD group scored significantly higher on the HAM-D ($t_{1.36}$= -8.07, $p < 0.001$), YMRS ($t_{1,36}$ = -2.92, $p < 0.01$), PANSS ($t_{1,36}$ = -4.34, $p < 0.001$) and childhood trauma questionnaire ($t_{1,35}$ = -6.99, $p < 0.001$) than the control group. All participants showed good engagement with the fMRI task (99.4% response rate). Participant information is detailed in table 5.1.

	BPD			Healthy control		
Demographics	n	mean	SD	n	mean	SD
Age	20	35.8	8.6	16	34.8	9.6
IQ	20	114.8	7.9	16	114.5	6
CTQ	20	52.9	19.8	16	13.1	11.5
HAM-D	20	15.5	8.6	16	0	0
YMRS	20	2.1	3.1	16	0	0
PANSS above baseline	20	2.6	2.5	16	0	0
ZAN-BPD	20	13.7	6.7	16	0	0
Medication	n	%				
Antipsychotic medication	12	60				
Antidepressant medication	15	75				
Comorbid diagnoses	n	%				
Total	17	85				
Depression	4	20				
Bipolar affective disorder ii	4	20				
Eating disorder	3	15				
PTSD	2	10				
OCD	2	10				
Other	2	10				

Table 5.1. Participant information

Brain activation to fearful faces

Across all participants, there were significant bilateral increases in activation when viewing fearful compared to neutral faces in the fusiform gyrus bilaterally (right $p < 0.001$, $K_E = 401$, $Z = 4.21$, co-ordinates 30, -82, -2; and left $p = 0.001$, $K_E = 240$, $Z = 5.34$, co-ordinates left -27, -82, -2), and amygdala bilaterally (within amygdala small volume correction, right $p = 0.04$, $K_E = 7$, $Z = 3.25$, co-ordinates 18, 4, -20; and left $p = 0.02$, $K_E = 17$, $Z = 3.54$, co-ordinates -24, -10, -14). There was also significant activation in the medial frontal gyrus ($p = 0.003$, $K_E = 192$, $Z = 4.41$, co-ordinates 42, 11, 25). Comparing activation between groups, significantly greater BOLD responses were noted in control participants than in those with BPD in the left cuneus ($p = 0.03$, $K_E = 238$, $Z = 3.72$, co-ordinates -18, -88, 7) to fearful versus neutral faces (figure 5.2). This group difference was investigated further, by comparing activation in response to neutral faces and activation in response to fearful faces with baseline activation – an average of activity across the entire task. Analysis revealed non-significant FWE corrected clusters of increased activity in fear faces v baseline ($p = 0.261$, $K_E = 129$, $Z = 3.60$, co-ordinates -18, -88, 4) and neutral faces v baseline ($p = 0.668$, $K_E = 72$, $Z = 3.40$, co-ordinates -18, -88, 4) in the cuneus in control participants compared to those with BPD (figure 5.3).

Brain activation to disgusted faces

Across all participants, increased activation was present bilaterally in the fusiform gyrus in response to disgusted compared to neutral faces; however activation did not reach significance (right p uncorrected = 0.305 and corrected = 0.986, K_E = 87, Z = 3.13, co-ordinates 48, -70, -5; and left p uncorrected =0.051 and corrected = 0.513, K_E = 87, Z = 3.24 co-ordinates -39, -61, -11).

Between groups, increased activation was found in the right parahippocampal gyrus, extending into the insula (confirmed by SVC, see figure 5.1), in those with BPD compared to healthy controls; however this cluster did not survive FWE correction (p = 0.189, K_E = 146, Z = 3.98, co-ordinates 30, -49, 10).

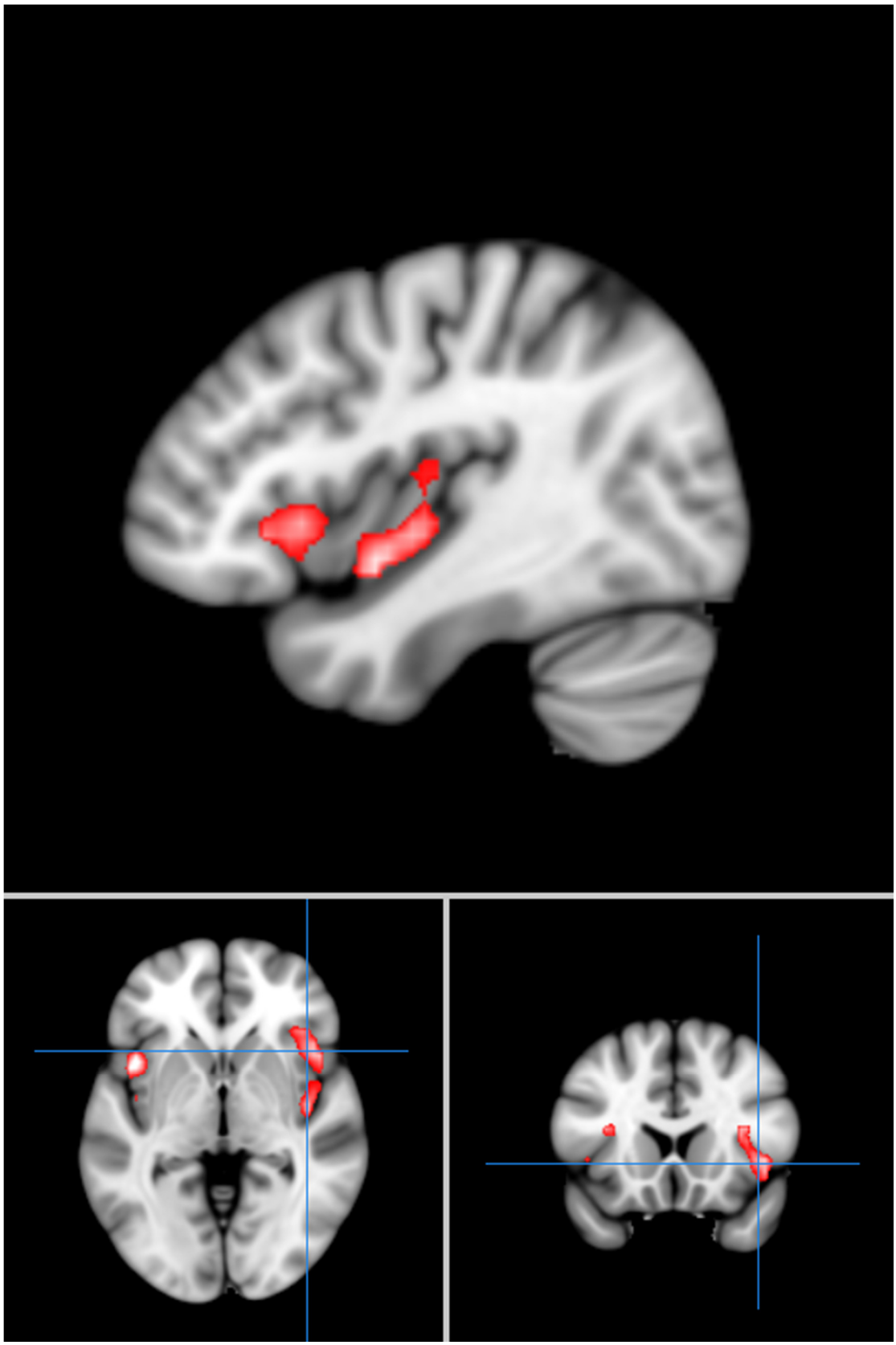


Figure 5.1. Greater (non-significant) insula activation in BPD compared to control in response to disgusted vs neutral facial expressions.

Effect of childhood experience

We next investigated the relationship between experience of childhood trauma, as measured by the childhood trauma questionnaire, and brain activation to emotional faces in those with a diagnosis of BPD. We specifically focussed on childhood experiences of physical abuse and emotional abuse based on previous behavioural data showing that these areas of childhood experience specifically had an effect on later responses to emotional faces, a finding that was not replicated with other subscales of the CTQ (see chapter 3).

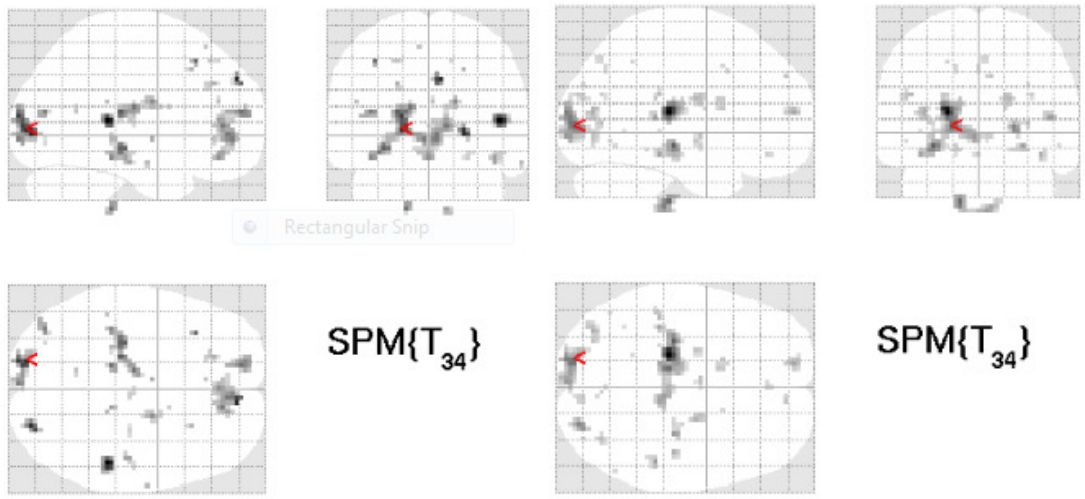
Regression of scores for prior physical abuse taken from the childhood trauma questionnaire against brain activation to fearful (versus neutral) faces revealed a network of brain activation related to increased physical abuse scores in BPD. Increased activation as a function of severity of prior physical abuse was found in the medial frontal gyrus ($p = 0.04$, $K_E = 240$, $Z = 3.82$, co-ordinates -24, 44, -2), pulvinar ($p = 0.007$, $K_E = 348$, $Z = 3.93$, co-ordinates -3, -25, 13), and cerebellum ($p = 0.03$, $K_E = 246$, $Z = 3.66$, co-ordinates 6, -52, -17) (figure 5.4A). Following application of a midbrain/ ventral striatum mask (Romaiuk et al 2010) significant activation was also noted in the midbrain ($p = 0.04$, $K_E = 82$, $Z = 3.66$, co-ordinates -6, -16, -14) (figure 5.4B). The whole-brain threshold was $P<0.005$ for all analyses. The relationship between physical abuse and midbrain activation remained significant after controlling for other CTQ subscales.

No significant correlation was identified between activation to disgusted faces and either physical abuse or emotional abuse as measured by the CTQ in BPD.

Brain activation to fearful faces and correlation with psychotic symptoms

We sought to determine whether increased midbrain activation in participants with BPD who had suffered physical abuse in childhood was related to current psychotic symptoms. Analysis of extracted data for the peak voxel of activation within the midbrain within the BPD group showed a significant correlation with reported positive psychotic symptoms as assessed by the PANSS ($p < 0.05$, $r = 0.45$, $n = 20$), with a particularly strong association seen between midbrain activation and the PANSS item for persecutory beliefs (P6). No association was seen between peak activation in the pulvinar, medial frontal gyrus or cerebellum and psychotic symptoms.

Figure 5.2. Brain sections showing greater activation in the right cuneus in the control group compared to the borderline personality disorder group, in response to fearful versus neutral faces.



A B

Figure 5.3. Greater activation in controls compared to BPD when viewing neutral faces compared to baseline (A) and fear faces compared to baseline (B).

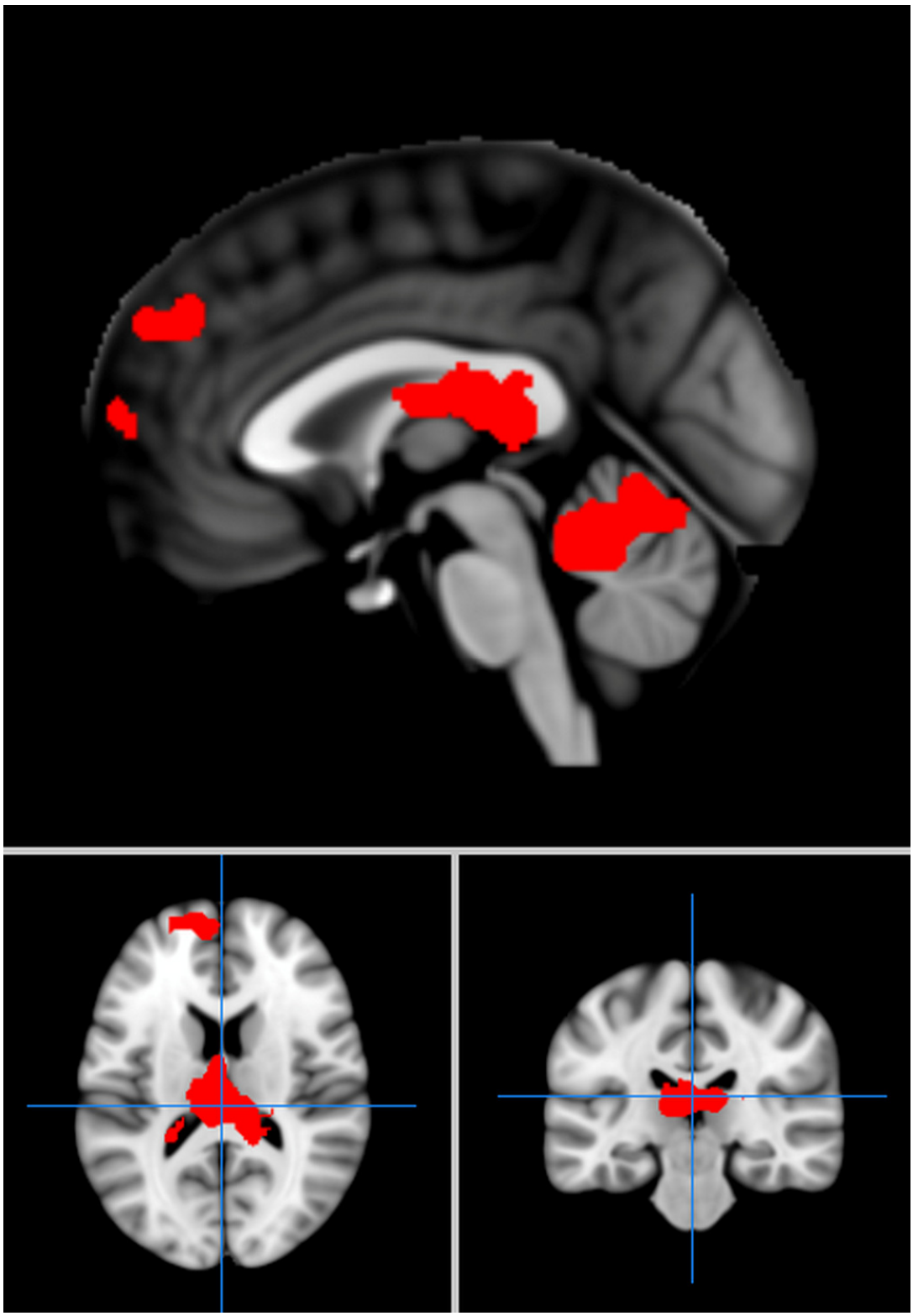


Figure 5.4A. Brain sections showing increased activation in medial frontal gyrus and cerebellum in response to fearful faces, which correlated significantly with childhood physical abuse, as, assessed by the CTQ

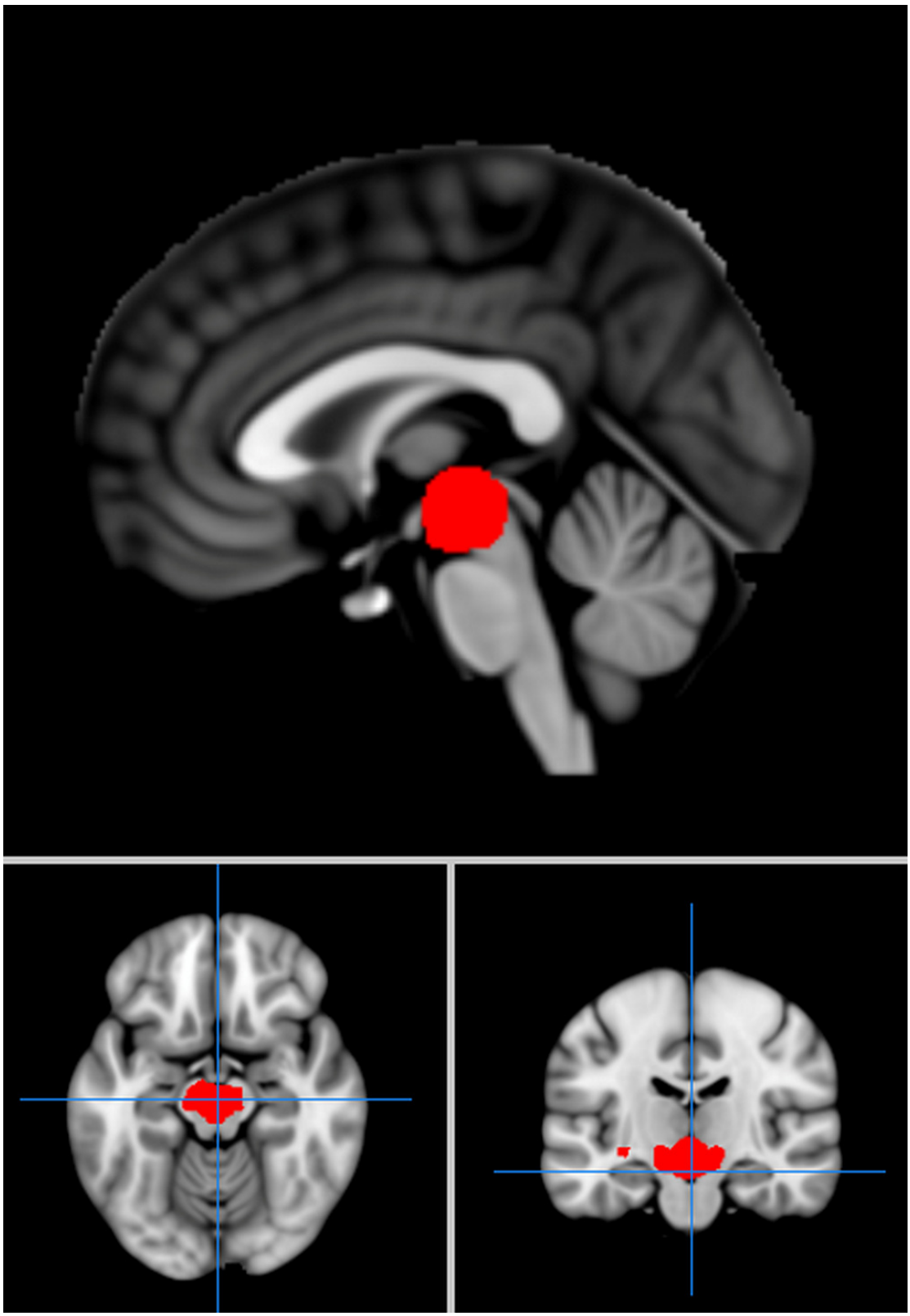


Figure 5.4B. Brain sections showing increased activation in midbrain in response to fearful faces, which correlated significantly with childhood physical abuse, as assessed by the CTQ.

5.4. Discussion

We have investigated brain responses to fearful and disgusted facial stimuli in individuals with BPD, and their relationship to self-reported experiences of childhood trauma and psychotic symptoms. Significant group differences in brain activation between participants suffering from the disorder and controls viewing fearful faces were restricted to the cuneus. In response to disgusted faces, no significant activation differences between groups was evident, however some increase in right parahippocampal gyrus and insula activation was observed.

Within the BPD group a strong relationship was observed between childhood experiences of physical abuse and greater activation of the midbrain, medial frontal gyrus, pulvinar and cerebellum to fearful stimuli. Midbrain activation to fearful faces was additionally correlated with severity of current psychotic symptoms, especially persecutory beliefs. These results support the view that early trauma can lead to long-lasting changes in brain responses to emotional stimuli. Although it is not possible to ascertain from the current study whether this effect is specific to BPD, such changes may contribute to the development of psychotic symptoms in adulthood, particularly at times of negative emotional stimulation.

The lack of significant findings in the disgusted vs neutral faces task was surprising, as results from previous work showed that emotional faces depicting disgust were least well recognised by our BPD group, and scores were strongly correlated with CTQ scores, in particular physical abuse and emotional abuse (see chapter 3). No previous studies were identified which specifically investigated disgust processing in BPD using fMRI, and it may be that group differences are not detectable using this method. However, a trend towards significance was identified in response to disgusted compared to neutral faces in the right parahippocampal gyrus and insula. The insula is reported to be specifically activated in response to disgust (Fusar-Poli et al 2009, Jabbi et al 2008, Sprengelmeyer et al 1998, Phillips et al 1997). This finding is thereofe in keeping with previous behavioural studies, which suggest dysfunction in disgust recognition and processing in BPD (Daros et al 2013, Unoka et al 2007), and suggests that there may be some insula dysfunction present in those with a diagnosis of BPD. In future, increasing the length of the fMRI task, as well as increasing sample size to improve power may allow significant activation differences between groups to be detected.

Direct comparison of brain activation in participants with BPD compared to controls viewing fearful faces revealed group differences in the activity of the cuneus. This difference may be attributed to the role of the cuneus in visual processing, as the heightened responsiveness to threat reported in BPD may lead to a hyper-attentiveness to such visual cues as those presented, which could be perceived as negative, or threatening. However, previous studies

involving BPD populations have also reported decreased activation (Jeungling et al 2003) and reduced functional connectivity (Wolf et al 2011) of the cuneus in this disorder. The cuneus is believed to play a role in theory of mind – the ability to attribute mental states to others – and studies involving healthy populations have revealed increased activity in this region during tasks involving theory of mind (Vrticka et al 2013, Vollm et al 2006). Taken together with our results, these findings suggest that cuneus dysfunction may contribute to deficient emotional processing in BPD. Notably, altered cuneus structure has also been associated with suicidality (Giakoumatos et al 2013), which is greatly increased in those with a diagnosis of BPD compared to the general population (Lieb et al 2004). Although the present study did not identify a link between cuneus function and suicidality (data not shown), it may be that altered activation in this region may contribute to risk for self-harm in the disorder.

Previous studies have identified a relationship between childhood trauma and altered emotion regulation, as well as behavioural responses to emotional stimuli in BPD (Vollm et al 2006). Childhood adversity has also been strongly associated with the development of symptoms of the disorder, and more generally with the development of psychotic symptoms across a range of disorders (Ball and Links 2015, Varese et al 2013, Bierer et al 2003). We investigated the relationship between childhood adversity and brain responses to emotional stimuli in participants with BPD. Using this analysis we identified a significant association between brain activation in a network of regions including the midbrain, medial frontal gyrus, pulvinar and cerebellum, and

previous experience of physical abuse as measured by the childhood trauma questionnaire.

The midbrain is the key site of dopaminergic afferents to the limbic system and is known to be involved in emotion processing (Friedel 2004). Dysfunction of this brain region is widely theorised to contribute to the development of psychotic symptoms in schizophrenia (Howes and Murray 2013, Tost et al 2010). The present results suggest that, in patients with BPD, childhood physical abuse correlates with an increased response of the midbrain to fearful emotional stimuli. We also found that individuals with BPD, who experienced childhood physical abuse, may be particularly vulnerable to the development of psychotic symptoms in adulthood. These findings suggest that there may be some link between childhood adversity, midbrain activation and psychotic symptoms in adulthood in BPD; and further investigation could potentially provide some biological rationale for the use of antipsychotic medications to ameliorate psychotic symptoms in the disorder (Montgomery 1987). However fMRI is only an indirect measure of dopamine system activation and the results would be strengthened by future studies using more direct measures such as positron emission tomography.

The present study identified additional areas of increased BOLD activation in response to fear versus neutral faces that correlated significantly with physical abuse in the BPD group. Greater activation was observed in the pulvinar, which is believed to be responsible for relaying fear information to the amygdala

(Pessoa and Adolphs 2010). A study with healthy volunteers found that the pulvinar was activated specifically in response to fearful faces (Vuilleumiere et al 2003) highlighting its importance in fear responses. The increased pulvinar activation observed in the current study may indicate a heightened fear response in individuals with BPD who suffered physical abuse in childhood. This is in keeping with previous work, which found that those with this diagnosis tended to judge neutral social cues as more threatening compared to controls (see chapter 3). The correlation of activation of the cerebellum to emotional stimuli with physical abuse is likely to reflect the increasingly recognised role of the cerebellum in processing affective and social information, and in particular in fearful emotion processing (Strata et al 2014, Schmahmann and Sherman 1998). The frontal gyrus has been implicated as being involved in facial emotion processing, particularly in differentiating between neutral faces and those showing emotion (Amting et al 2010), and increased activation in this area may reflect heightened sensitivity to emotional compared to neutral facial expressions.

The specificity of the current findings to physical abuse and fearful faces warrants further comment. It is possible that physical abuse has a particularly strong relationship with subsequent brain responses to fear-related stimuli in adulthood, resulting in the activation of limbic/motivational "salience" networks. However an alternative possibility is that physical abuse is most clearly recalled by participants, or has greater discriminatory power due to the range of responses reported. However as other behavioural changes, such as

social judgement decision biases, are more strongly correlated with sexual abuse in BPD (see chapter 3) we suggest that physical abuse may have a particular impact on fear processing in adulthood.

The present study demonstrates a significant association between childhood trauma and brain activation in BPD, and suggests a link between childhood physical abuse and psychotic symptoms in adulthood. To the authors' knowledge, this is the first time such correlations have been identified in a BPD population. These results may help explain the sensitivity of many individuals with the disorder to negative emotional stimuli, and in particular the tendency of sufferers to develop psychotic symptoms at times of emotional stress. Altered midbrain activation may also underlie the response to antipsychotic treatment seen in patients with BPD, although this requires further investigation. The results also support the use of early psychological interventions in individuals with this diagnosis to ameliorate negative responses to environmental stimuli, and highlight the importance of managing emotional stressors in sufferers. They illustrate the key role of early life experience in modulating midbrain activation, which may be of relevance to a range of psychiatric disorders, particularly those in which psychotic symptoms are a significant feature.

There are some limitations to the study, which should be acknowledged. First, the majority of participants in the BPD group were taking medication at the time of the study. It is possible, though unlikely, that medication effects may have contributed to the group difference in activation noted in the cuneus and

in the correlations noted between brain activation and childhood trauma. However, the likelihood of this is very low, given the variation of medications in use across participants and the specific effects of childhood abuse seen in the within-group correlation analyses. The variation of medications and doses used, and that some participants were taking more than one type of medication may also have some bearing on the reported results. Unfortunately, it is not possible to control for this in the analysis. In addition, a substantial number of those with a diagnosis of BPD also had secondary, comorbid diagnoses at the time of study. Again, the range of comorbid diagnoses is such that the type and intensity of psychiatric symptoms experienced by individuals within the group is likely to vary dramatically; however this in itself is a feature of a BPD diagnosis, with any two individuals very unlikely to present with the same symptoms. Finally, further investigation is required, ideally using larger sample sizes, in order to better determine the potential role of the midbrain in the development of psychotic symptoms in BPD. Similarly, this relationship in other psychiatric disorders should be investigated, in order to elucidate if it is specific to BPD, or present in mental illness more generally.

Nonetheless, the present findings highlight the damaging effects of adverse childhood experiences into adulthood, and support early intervention for those at risk of developing BPD. Early intervention strategies, for example engagement with families or carers, family intervention and tailored psychotherapy may prove effective. Our results also provide some support for the use of drugs targeting the dopamine system in BPD, but more research is

needed (Olabi and Hall 2010). Overall, the study emphasises the importance of continuing biological research into BPD, in order to further our understanding of the condition and to identify suitable therapeutic or alternative therapies for those suffering from the disorder.

6. Functional connectivity in BPD in response to emotional faces

6.1. Introduction

In order to process information and carry out cognitive tasks, different areas of the brain must cooperate and work together. Brain regions and structures activate together to form functional networks, responsible for perception, actions, cognition and behaviour (Park and Friston 2013). Several functional networks can be commonly identified in the human brain, with three large-scale networks believed to be paramount in cognitive and emotional information processing (Chen et al 2013). These are the central executive network (CEN), which comprises the dorsolateral prefrontal cortex and posterior parietal cortex, the default mode network (DMN), made up of structures within the medial prefrontal cortex and the medial temporal lobe, and the salience network (SN), which includes the insula and anterior cingulate cortex. Each of these networks has been identified as activated in response to specific tasks, for example the central executive network is activated during executive functions, such as problem solving and reasoning (Goulden et al 2014); the DMN is involved in internally focussed tasks, or tasks involving understanding others (Li et al 2014, Buckner et al 2008); and the SN is activated during wakeful rest,

or behaviourally salient events (Ham et al 2013). However, interaction between the three networks is necessary for complex information processing, and studies have reported that the DMN is under inhibitory control from the CEN (Chen et al 2014), and that there appears to be a "switching" between these networks, which is driven by the SN (Goulden et al 2014, Sridharan et al 2008). Therefore dysfunction in one network may have implications for wider information processing, and such deficits are common in psychiatric disorders, including BPD (Menon 2011, Buckner et al 2008).

Functional connectivity data can be acquired using a number of neuroimaging modalities, including fMRI and positron emission tomography (PET) scanning. Following fMRI data acquisition, one of three analysis methods is commonly used, namely independent component analysis (ICA), dynamic causal modelling (DCM) or psychophysiological interactions (PPI). All methods estimate the functional connectivity between brain areas; however in contrast to seed and hypothesis based approaches, such as PPI and DCM, no prior assumptions are necessary for ICA. PET measures glucose usage in the brain, which can be used to determine the extent to which brain areas are coupled, or activated together.

Several previous neuroimaging studies of BPD have revealed abnormal function in the amygdala in those with the disorder, in response to a variety of tasks and stimuli (Mitchell et al 2014, Mier et al 2013, Guitart-Masip et al 2009, Minzenberg et al 2007, Donegan et al 2003). In recent years, a growing number of studies have investigated not just function, but functional connectivity in

BPD, in order to gain a better understanding of the neural correlates of its symptomatology.

In keeping with the previous literature, several studies have indicated altered amygdala connectivity in those with a diagnosis of BPD compared to controls. Cullen et al (2011) found altered functional connectivity in BPD compared to control participants between the amygdala and the cingulate cortex, thalamus and caudate in response to neutral, masked fear and overt fear facial stimuli. Functional connectivity within the DMN, which includes the amygdala, has also been reported as aberrant in resting state studies of BPD (Krause-Utz et al 2014, Doll et al 2013, New et al 2007), and also with application of painful heat stimuli (Kluetch et al 2013). Abnormal functional connectivity has also been found in the SN in BPD (Krauze-Utz et al 2014), and Doll et al (2013) reported abnormal functional connectivity in all three of the DMN, SN and CEN during resting state, and in particular a shift in the way these networks interact, with decreased CEN and increased SN connectivity.

Although few functional connectivity studies of BPD so far have included stimuli in their paradigms, those which have tended to utilise negative stimuli, including fear faces, painful stimuli and negative emotionally arousing images (Kluetch et al 2013, Neidtfeld et al 2012, Cullen et al 2011). Previous work suggests that individuals with a diagnosis of BPD display deficits in performance on behavioural tasks that include emotional stimuli, and have particular difficulty with negative emotional stimuli (Mitchell 2014, Unoka et al

2007, Wagner and Linehan 1999; for more detail see chapter 1). A substantial body of work has focused solely on brain activation in response to facial emotion, clearly illustrating differences in the processing of this type of stimuli in those with BPD compared to healthy controls (Mitchell 2014 for review, or for more information see chapter 1). It seems evident, then, that there may also be differences in functional connectivity between groups in response to this kind of stimuli; however so far relatively little work has investigated this.

Thus while there does appear to be a consensus among researchers that functional connectivity in BPD is significantly different than that of healthy control comparisons in a number of regions and networks, a clear picture of this dysfunction, when it occurs and why connectivity may be altered has not yet been developed. Here, we aim to further the understanding of functional connectivity in BPD by utilising a task of facial emotion, specifically fear and disgust, in a group of participants with the diagnosis as well as a group of healthy controls. Emotional faces depicting fear and disgust were specifically selected based on previous work, which demonstrated that these emotions were least well recognised by our participant sample of those with a diagnosis of BPD (see chapter 3). In addition, the processing of fear is known to primarily involve the amygdala (Adolphs 2008, Phan et al 2002, Buchel and Dolan 2000, Morris et al 1996), and disgust processing primarily activates the insula (Jabbi et al 2008, Sprengelmeyer et al 1998, Phillips et al 1997). Connectivity was compared between groups in the DMN, SN and CEN, all of which should

normally be recruited in the processing of our chosen stimuli, and have been implicated as aberrant in BPD.

We expected to find a significant difference in functional connectivity in the DMN, SN and CEN in those with a diagnosis of BPD compared to healthy control participants. Given the well-known involvement of the amygdala in fear processing, and the insula in disgust processing, and since amygdala and insula are components of the DMN and SN, respectively, we hypothesised that any abnormalities in functional connectivity in response to our task would be particularly apparent in these networks.

6.2. Methods

Participants

Twenty individuals with a diagnosis of BPD were recruited from outpatient populations. Diagnosis of BPD (DSM-IV criteria) was established using the SCID-II. The BPD group consisted of 17 females and 3 males, mean age (35.6) and mean IQ (114.8, assessed by the National Adult Reading Test). Of these, 12 were being treated with antipsychotic medication, and 15 with antidepressant medication. Sixteen healthy control participants were recruited from community volunteers, comprising 14 females and 2 males, mean age (35.7) and

mean IQ (113.3). Exclusion criteria for all participants included a history of bipolar I disorder or schizophrenia, current alcohol or drug dependency, or any neurological illness. Additionally, exclusion criteria for healthy control participants included a diagnosis of BPD or other personality disorder. All participants were aged between 18 and 53. Co-morbid psychiatric diagnoses were established using the SCID-I interview and case note review.

The study was approved by the Lothian Research Ethics Committee. All participants gave written informed consent following a period of at least 24 hours consideration with access to the study information sheet. All participants had the opportunity to discuss the study, and understood that they were free to withdraw at any time. Participants who withdrew from the study were not disadvantaged in any way.

FMRI task

In the scanner, participants performed a task that involved viewing a photograph of a face on a computer screen, and selecting whether they thought the face was male or female, indicated by pressing the corresponding response button. To ensure that participants had a full understanding of the task, screen-shots of the images used were shown to each person before entering the

scanner and a complete explanation of the task was provided. Faces were chosen from the Ekman series of emotional faces (Ekman and Friesen 1976) and displayed either a fearful, disgusted or neutral expression. The task was spit into two, with one showing disgusted and neutral faces, and the other showing fearful and neutral faces. Each task was made up of six blocks, with each containing six images of faces. Within each block, all of the faces displayed the same emotion –neutral, disgusted or fearful – with half being female and half male, shown in a random order. Faces appeared on the screen for 5 seconds, and a response (male or female) had to be made within this time to be registered, providing a measure of compliance with the task. Two versions of the task were used, one showing neutral faces in the first block, and the other showing emotional faces in the first block. The version of the task shown to each participant was randomised.

fMRI data acquisition

Imaging data was acquired using a 3T Siemens Magnetom Verio Syngo MR scanner. Functional imaging scans were acquired using the following parameters: repetition time (TR) 1560 ms, echo time (TE) 26 ms, flip angle 66°, 26 slices (slice thickness 5 mm), field of view (FOV) 220 x 220 mm, voxel size 3.5 x 3.5 x 5 mm.

fMRI data analysis

Task analysis was completed separately for each of the disgust and neutral, and fear and neutral components. Images were analysed using FMRIB Software Library (FSL, Oxford). Before preprocessing, the first six images were discarded. Motion correction was applied using MCFLIRT (Motion Corrected FMRIB's Linear Image Registration Tool; Jenkinson et al 2002), and all non-brain tissue was removed using the brain extraction tool (BET; Smith 2002). The data smoothed with a Gaussian kernel (6mm full width at half maximum) and finally a high-pass temporal filter equivalent to 100s was applied. Patterns of functional connectivity were then identified using ICA, as implemented by the MELODIC tool (Multivariate Exploratory Linear Decomposition into Independent Components; Beckmann and Smith 2004). Dual-regression analysis (Beckmann et al 2009) was performed in order to identify participant-specific time courses and spatial maps of functional connectivity. This process was completed in two steps. The first regressesd the group spatial maps into the dataset for each participant, creating a set of timecourses. These timecourses were then regressed back into the same participant datasets to create a specific spatial map for each subject.

6.3. Results

Demographics

There was no difference in age ($t_{1,36}$ = -3.82, p = 0.97) or IQ ($t_{1,31}$ = -0.56, p = 0.58) between groups. Five control participants did not complete the National Adult Reading Test and these individuals were excluded from IQ analysis. All participants showed good engagement with the fMRI task (99.4% response rate). Participant information is detailed in table 6.1.

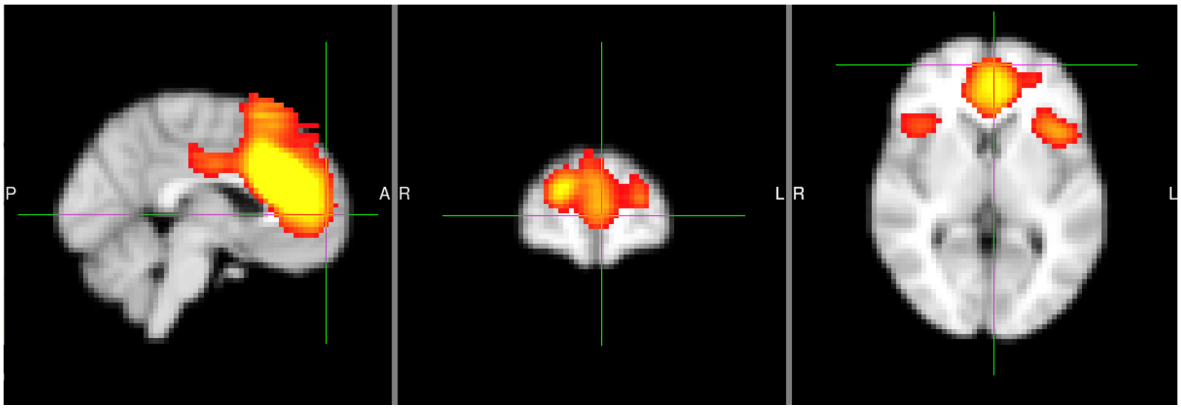
	BPD			Healthy control		
Demographics	n	mean	SD	n	mean	SD
Age	20	35.8	8.6	16	34.8	9.6
IQ	20	114.8	7.9	16	114.5	6
Medication	n	%				
Antipsychotic medication	12	60				
Antidepressant medication	15	75				
Comorbid diagnoses	n	%				
Total	17	85				
Depression	4	20				
Bipolar affective disorder ii	4	20				
Eating disorder	3	15				
PTSD	2	10				
OCD	2	10				
Other	2	10				

Table 1. Participant information

Independent component analysis

Using ICA, 25, 27 and 30 components were extracted per participant in three separate runs. The CEN, DMN and SN were identified from these, with the run of 27 components producing the clearest and most complete extraction of all three networks (figure 6.1.). Networks identified from the run of 27 components were selected for the remainder of the analysis, and each network was compared between groups for each task. No significant differences were identified between the BPD and control group in any network in response to either the fear and neutral, or disgust and neutral task.

A



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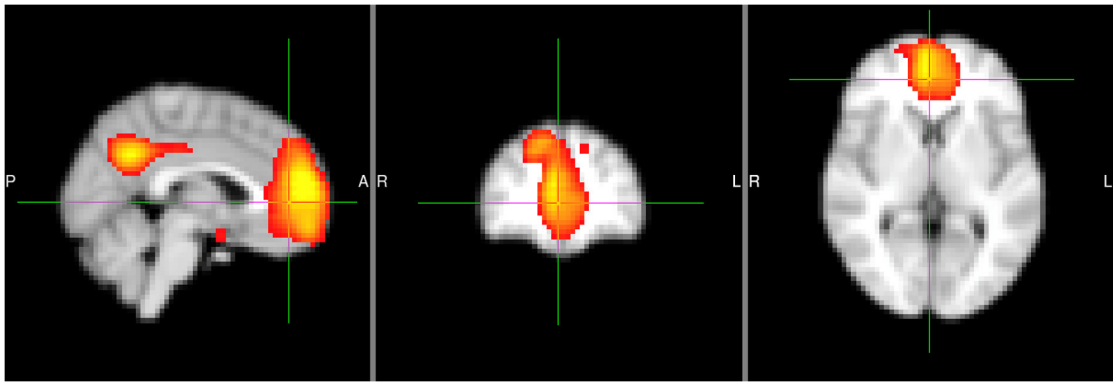

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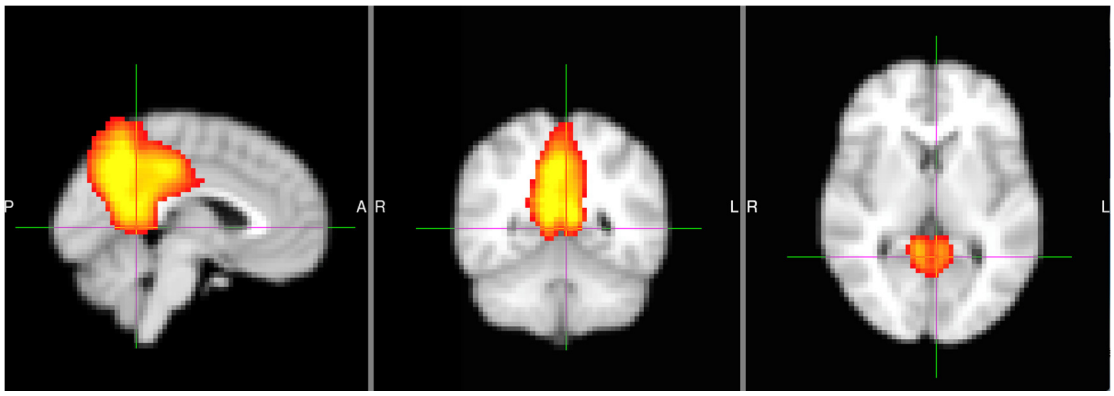
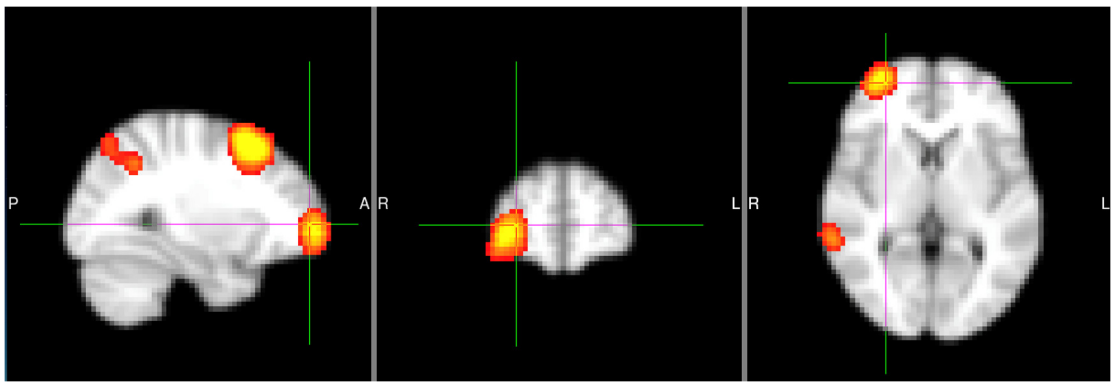


D



E

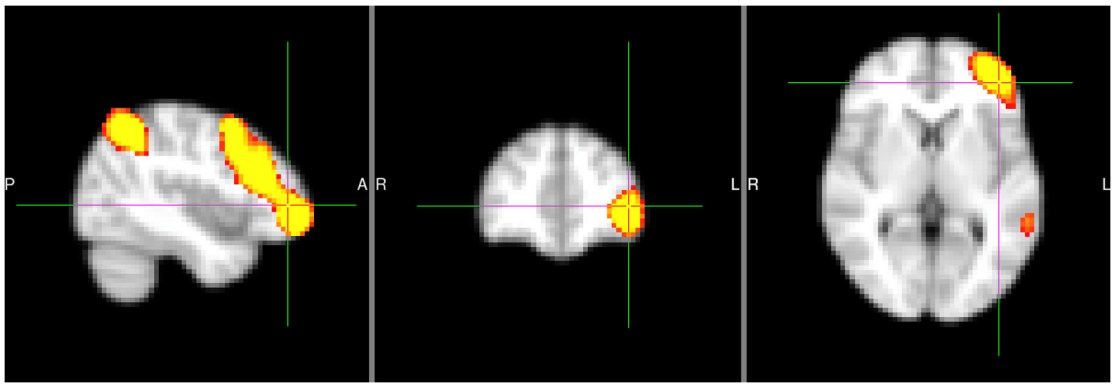


Figure 6.1. Brain activation maps showing A. anterior SN, B. anterior DMN, C. posterior DMN, D. right CEN, E. left CEN taken from ICA of 27 components

6.4. Discussion

The current study did not find any significant differences in functional connectivity in the CEN, DMN and SN between individuals with a diagnosis of BPD and healthy control participants in response to emotional faces. This result is in contrast to previous studies of functional connectivity in the disorder.

The present findings may differ from previous studies for a number of reasons. It may be that abnormalities in functional networks cannot be easily identified in response to specific, discrete emotional faces. It may also be that no differences in functional connectivity exist between those with BPD and healthy controls in response to, specifically, fearful or disgusted faces that are not attended to. This may be disputed, as Cullen and colleagues (2011) did report aberrant functional connectivity in their BPD group in response to masked fear

faces. However, both the experimental procedure and group demographics differed from the current study. Notably, Cullen et al recruited a very small sample size, with 12 participants in each group, and the mean age of these was far lower than in our sample (24.1 vs 34.8 BPD and 25.1 vs 34.8 control). Studies have identified age effects on grey matter volume in the amygdala in BPD (Hall et al 2010), as well as in functional connectivity in healthy participants (Ford and Kensinger 2014, Hoffstaedter et al 2014, St. Jacques et al 2009), so it is possible that such a variation in age could contribute to the contrasted findings between studies.

Limitations of the current study should also be acknowledged. First, the imaging data used for the ICA came from tasks that lasted for only five minutes each. This is a relatively short acquisition time, and may not provide enough information to detect any group differences. Second, within the same task, pictures of faces showed both fearful and neutral, or disgusted and neutral expressions. Previous studies of BPD have shown that different emotions are processed differently, and activate different brain areas (see Mitchell et al 2014, Daros et al 2013 for review, or see chapter 1), so including only one facial expression in future work may yield more reliable results. Third, the relatively small sample size may provide insufficient power to detect any differences in functional connectivity between groups. Finally, the majority of participants within the BPD group were taking medication at the time of study (75% antidepressant, 60% antipsychotic), so medication effects may be responsible for masking any

possible connectivity deficits. Studies have shown that antidepressant medication has a normalising effect on functional connectivity in the DMN in depression (Andreescu et al 2013), and dysthymia (Posner et al 2013). Alterations in functional connectivity following antipsychotic medication have also been reported in healthy controls (Klasen et al 2013) and in schizophrenic populations (review: Abbott et al 2013, Nejad et al 2012). Therefore, future studies should ideally include participants who are medication free although, practically, this may prove difficult.

In conclusion, although the current study did not identify aberrant functional connectivity in BPD, DTI analysis, which was carried out collaboratively on the same cohort, did reveal abnormalities in structural connectivity in the disorder. White matter tract integrity was found to be reduced in the cingulum and fornix in BPD compared to healthy controls; so connectivity differences do appear to be detectable in the current participants. The present findings indicate that there are no differences in functional connectivity in BPD, however we have identified a number of methodological limitations in the study. There may also be more localised changes in connectivity present in networks other than those investigated here. Employing other methods of functional connectivity analysis, such as PPI or DCM, may provide further insight into functional connectivity in those with a diagnosis of BPD.

Very few studies have investigated functional connectivity in response to stimuli

in BPD and, to the best of the author's knowledge, only one has utilised emotional faces. Taking into consideration the severe and debilitating emotional difficulties experienced by those with a diagnosis of BPD, further studies of functional connectivity and emotion could provide important insight into the neurobiology of the disorder. It would therefore be prudent to continue research in this area, but to address the identified methodological issues as much as possible in doing so. Only then can our understanding and treatment of BPD be meaningfully improved.

7. General Discussion

In the present work, we have demonstrated that individuals with a diagnosis of BPD have particular difficulties in social cognition, specifically emotion recognition and social judgements from faces. We have also shown that significant differences in brain function are evident in those with BPD compared to healthy control participants, particularly in areas related to emotion and salience processing, while structural changes are not so apparent. Furthermore, strong correlations exist between childhood trauma and both the symptoms and neurobiology of the disorder.

Our findings provide evidence for BPD as a brain disorder, showing that regions important in social and emotional processing are dysfunctional in the disorder, and likely account for the common and debilitating social difficulties experienced by those with a diagnosis. This has important implications for the way people with BPD are viewed and the stigma associated with the disorder. A diagnosis of BPD can lead to rejection by the mental health system (Paris 2007), and BPD has been referred to as a "wastebasket" diagnosis (Aronson 1985) – a non-specific description of something that does not really exist or cannot be explained physiologically. Studies such as those preceding, which can demonstrate real and significant biological differences between those with BPD and healthy controls can help to lessen this negative image of what is a very serious condition.

Neuropsychological findings

We employed two tests of social cognition to investigate the difficulties in this area in BPD. The first was a test of emotion recognition, whereby participants looked at photographs of faces and were asked to identify which emotion was being shown from a possible six – anger, disgust, fear, happiness, sadness, surprise. These six universally recognisable emotions were displayed beneath the photographs and participants were not time-limited in their responses, eliminating the possibility of time pressure effects on performance. Performance in the emotion recognition task was significantly different between groups, with the BPD group proving to be less well able to correctly identify facial emotion than the control group. In particular, those with BPD had a particular deficit in their recognition of disgust. Correlation analysis revealed a strong association with incidence of childhood trauma and emotion recognition. In particular, a significant positive correlation was revealed between disgust recognition and measures of physical abuse and emotional abuse.

Our emotion recognition results indicate that traumatic events in childhood can have a lasting effect, and appear to play a role in the development and symptoms of BPD in adulthood. This provides further evidence for a causal relationship between childhood trauma and BPD, supporting the conclusion reached by Ball and Links (2009) following analysis of the literature.

Disgust processing involves a number of brain regions, but the insula is particularly specialised in the recognition, experience and processing of this emotion (Fusar-Poli et al 2009, Jabbi et al 2008, Sprengelmeyer et al 1998, Phillips et al 1997). It may be the case that abnormalities in the structure and/or function of the insula could account for the particular difficulties in the recognition of disgust in BPD. Reduced insula grey matter volume has been previously reported in those who have experienced childhood trauma (Dannlowski et al 2012), however such a finding was not replicated in the current work. With so few studies having investigated insula structure in BPD, it is difficult to draw any conclusions, and it is impossible to say whether or not disgust recognition deficits are due to reduced insula volume. However, increased activation in the insula was observed in those with BPD compared to controls in response to disgusted faces in our sample. Therefore abnormal insula function may contribute to deficient disgust recognition in BPD.

The second neuropsychological test investigated social judgement in BPD. In this test participants viewed photographs of faces and were asked to make a judgement about each person based on one of six social dimensions – age, distinctiveness, attractiveness, intelligence, approachability or trustworthiness. We found that those with a diagnosis of BPD performed significantly worse than healthy controls in this test, and that the difference was driven by incorrect judgements of approachability and trustworthiness in the BPD group. Judgement bias in BPD was also negatively skewed, with participants more

likely to judge approachable faces as unapproachable and trustworthy faces as untrustworthy. Correlation analysis further revealed an association between judgements of approachability in BPD and childhood trauma, particularly with the sexual abuse subscale.

The amygdala has been implicated in the retrieval of socially relevant information (Somerville et al 2006) and judgements of trustworthiness (Winston et al 2002). This area is also key in threat detection and fear conditioning (Adolphs 2008, LeDoux 1998) to which judgements of approachability and trustworthiness are closely related. Therefore impairments in social judgement may be due to abnormalities in the amygdala in those with BPD. This idea is not supported by the current work, which reported no significant differences between groups in amygdala structure or function, although previous studies have found grey matter volume abnormalities in BPD (Ruocco et al 2012, Hall et al 2010, Nunes et al 2006).

Strikingly, the most robust finding from our neuropsychology tests was the impact that childhood trauma appears to have on symptoms of BPD in adulthood. The correlation between childhood trauma and social judgement scores is in keeping with the correlation found between CTQ scores and emotion recognition, providing compelling evidence that childhood trauma has an effect on later symptoms of BPD. Indeed, this finding was replicated in our fMRI findings, in which brain activation in areas involved in emotion processing correlated with incidence of abuse in childhood. The importance of childhood

trauma in the development of symptoms of BPD provides support for early interventions in the disorder, which have proved effective in a clinical sample (Chanen et al 2008). In particular, psychological therapies focussing on understanding oneself as well as others, such as mentalisation-based therapies, may prove helpful in ameliorating the distressing social difficulties in those with a diagnosis of the disorder.

Structural imaging findings

Brain structure in BPD was studied using MR imaging and VBM in SPM8. No grey matter volume differences were identified between those with a diagnosis of BPD and healthy control participants. This finding was in contrast to our hypothesis, that amygdala and insula volume would be altered from normal in our sample. This prediction was made based on our neuropsychology findings of deficits in the recognition of disgust and impaired judgements of approachability and trustworthiness. However, structural imaging studies in BPD to date have yielded varying results, and the current study is in support of those that reported no structural differences in these areas (Schmahl et al 2009, Tebartz van Elst et al 2007). There are several reasons for the variation in structural results between studies, including methodological issues and group demographics and power. However, DTI analysis, which was carried out collaboratively on the sample recruited here, did reveal structural differences in white matter tract integrity indicating that the current study did have sufficient power to detect structural differences between groups. It may be the case that

employing different structural imaging techniques would reveal structural changes other than those related to volume, such as shape and texture.

Functional activation imaging findings

Brain function in response to emotional faces was compared between individuals with a diagnosis of BPD and healthy control participants. While in the scanner participants completed two tasks, which involved looking at photographs of faces and deciding if each one was male or female. In one task, faces displayed disgusted expressions, and in the other task the faces showed fearful expressions.

We found that, in response to disgusted compared to neutral facial expressions, those with BPD showed a trend towards greater activation in the parahippocampal gyrus and insula than controls. This finding is in keeping with our neuropsychology study, which found impaired disgust recognition in the BPD group, and suggests that such impairment may be due to insula dysfunction in the disorder. Indeed, insular hyperactivation has previously been found in studies of BPD in response to negative emotional stimuli (Ruocco et al 2012), and it is possible that such activation may reflect compensatory brain activation changes in this region. While only a trend towards significance was found following FWE correction in the current study, our modest sample size may have prevented activation in this area from reaching significance. Replicating

the task used with a larger sample, and perhaps increased task length would help us to understand whether or not dysfunction in the insula is present in those with BPD.

In response to fearful compared to neutral faces, significantly increased activation was found in the cuneus in those with a diagnosis of BPD compared to healthy control participants. Abnormal functional activation in the cuneus in BPD has previously been reported in response to memories of abandonment (Schmahl et al 2003), and aberrant functional connectivity in this area has also been found in the disorder (Wolf et al 2011, Jeungling et al 2003). Abnormalities in the cuneus do appear to be a feature of BPD, in particular increased activation in response to emotionally arousing stimuli.

Correlation analysis using CTQ scores revealed significant correlations between childhood physical abuse and activation in the medial frontal gyrus, pulvinar and cerebellum - regions involved in emotion and fear processing - as well as in the midbrain following SVC. Midbrain activation was found to further correlate with psychotic symptoms in those with a diagnosis of BPD, indicating a potential link between adverse events in childhood, midbrain function and the development of psychotic symptoms in adulthood, although this requires further investigation. Our functional activation results provide further support for our neuropsychology findings, that childhood trauma is linked to symptoms of BPD, and is likely to be a causal factor. If adverse events in childhood have such an effect on not only the symptoms, but the development of BPD, the idea

of early interventions in the disorder becomes even more relevant, particularly in a preventative role.

Overall, we found that functional abnormalities in BPD are far greater than structural changes. We decided to further explore function in those with a diagnosis of BPD compared to healthy controls by conducting functional connectivity analysis, in the hope of shedding further light on brain changes in the disorder.

Functional connectivity findings

Functional connectivity in the CEN, SN and DMN in those with BPD and a group of healthy controls was explored using fMRI data and ICA in FSL. The fMRI data was collected during two tasks during which participants were presented with emotional facial stimuli (disgusted and neutral faces, or fearful and neutral faces).

No significant differences between groups was noted in functional connectivity analysis of those with BPD and healthy control participants in either task. Functional connectivity differences my not be present in response to discrete emotions in the CEN, SN or DMN in the disorder. Alternatively, methodological issues of the current study were identified, which may be responsible for the lack of significant findings. However, it could also be that employing a seed or

hypothesis driven technique would reveal connectivity abnormalities in specific regions of interest, such as the amygdala and insula.

General limitations

There are some important limitations of the work in general, which should be noted. A large majority of individuals in the BPD group, in both the pilot and main study, were taking antipsychotic and/or antidepressant medication at the time of testing and scanning. It is possible that medication effects could confound the results presented here, as such medicines not only alleviate the symptoms of the disorder, but can also alter brain structure and function. Medication effects are extremely difficult to control for, due to the variety of drug type, dose and combinations present. Ideally, recruitment of as many drug-free participants as possible would help minimise this problem. However, in the current work, even if all participants were free from medication at the time of study, there is still the issue of the diverse range and combination of symptoms possible for a diagnosis of BPD to be given. As mentioned in chapter 1, a total of 256 different symptom combinations can result in a BPD diagnosis, with symptoms including depression, mania, psychosis.

There is also the issue of comorbidity, with several participants having an active diagnosis not just of BPD, but of other conditions including eating disorders, PTSD, depression. Each of these conditions in itself has been associated with

brain changes, for example reduced functional connectivity in anorexia nervosa (Ehrlich et al 2015), grey matter volume reductions in PTSD (O'Doherty et al 2015), not to mention the myriad studies of depression that have revealed structural, functional and connectivity abnormalities, including a number of studies of facial emotion processing (Fusar-Poli et al 2009). It is therefore impossible to state with confidence that the deficits and brain changes reported here are definitively associated with BPD, and have not been confounded by other disorders and symptoms. However, given the variety of symptoms associated with BPD, it is difficult in any case to associate a particular neuroimaging or behavioural finding with the disorder per se. Rather, it may be that particular symptoms or subtypes of BPD are more associated with specific brain or behavioural changes than others.

It should also be noted that in both the pilot and main study, participants in the control group consistently scored zero on the HAM-D, YMRS and BPD criteria. While it could be argued that such scores are desirable for controls, it should be considered that this sample may not be an accurate representation of the general population, many of whom will have experienced some symptoms of depression or mania in their lifetime. It is possible that scores of zero on these measures may have led to an overestimation of group differences. However, the significant results reported in the preceding work are robust, so this is unlikely.

Conclusions and future directions

The current work has revealed severe difficulties in social cognition in BPD, as well as functional activation abnormalities in brain regions key to the processing of social information. Childhood trauma, in particular physical abuse, was also shown to be highly correlated with both the behavioural and functional abnormalities reported. Overall, the present results suggest that BPD is associated not with major changes in brain structure, but with functional changes in a network of areas key to emotion processing, which may contribute to some of the key symptoms of the disorder.

Future studies researching BPD should take care to ensure that information regarding particular symptoms and symptom severity of the disorder is collected from each participant with a diagnosis of BPD. In this way, particular diagnostic criteria may be linked with specific difficulties and brain abnormalities. It may be the case that different subtypes of the disorder contribute to some of the inconsistencies in the literature, but it is not possible to reach any conclusions based on existing work. A more complete understanding of BPD and its subtypes may allow for more personalised treatments to be prescribed or developed, helping to reduce the current stigma of the disorder. It is important that research in this area should continue, and that both the scientific and wider communities understand that BPD is a brain

disorder, that there are biological reasons for its symptomatology and that sufferers can be helped with the correct management.

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9. Appendices

CTQ

These questions ask about some of your experiences growing up as a child and teenager. For each question place an X in the box under the response that best describes how you feel.

When I was growing up…	Never true	Rarely true	Sometimes true	Often true	Very often true
1 I didn't have enough to eat.					
2 I knew there was someone there to take care of me and protect me.					
3 People in my family called me things like "stupid", "lazy" or "ugly".					
4 My parents were too drunk or high to take care of the family.					
5 There was someone in the family who helped me feel I was important or special.					
6 I had to wear dirty clothes.					
7 I felt loved.					
8 I thought that my parents wished I had never been born.					
9 I got hit so hard by someone in my family that I had to see a doctor or go to hospital.					
10 There was nothing I wanted to change about my family.					
11 People in my family hit me so hard it left me with bruises or marks.					
12 I was punished with a belt, a board, a cord or some other hard object.					
13 People in my family looked out for each other.					
14 People in my family said hurtful or insulting things to me.					

When I was growing up…	Never true	Rarely true	Sometimes true	Often true	Very often true
15 I believe I was physically abused.					
16 I had the perfect childhood.					
17 I got hit or beaten so badly that it was noticed by someone like a teacher, neighbour or doctor.					
18 I felt that someone in my family hated me.					
19 People in my family felt close to each other.					
20 Someone tried to touch me in a sexual way, or tried to make me touch them.					
21 Someone threatened to hurt me or tell lies about me unless I did something sexual with them.					
22 I had the best family in the world.					
23 Someone tried to make me do sexual things or watch sexual things.					
24 Someone molested me.					
25 I believe that I was emotionally abused.					
26 There was someone to take me to the doctor if I needed it.					
27 I believe I was sexually abused.					
28 My family was a source of strength and support.					